



IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re: US Patent No. 5,202,333  
Issued: April 13, 1993  
Application No: 07/704,565  
Filed: May 22, 1991  
Inventors: Jacob Berger *et al.*  
Assignee: Roche Palo Alto LLC  
For: Tricyclic 5-HT<sub>3</sub> antagonists

enclosure  
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**Application for extension of patent term under 35 USC 156(d)(1)**

Roche Palo Alto LLC, a Delaware limited liability company, is the assignee of the entire interest in US Patent No. 5,202,333, issued on April 13, 1993, for Tricyclic 5-HT<sub>3</sub> antagonists, by an assignment from the inventors, Jacob Berger *et al.*, to Syntex (U.S.A.) Inc. recorded on September 13, 1991 at Reel 005829, Frame 0428; the subsequent merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC, recorded on July 9, 2003 at Reel 013782, Frame 0352; and the subsequent change of name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC, recorded on July 10, 2003 at Reel 013782, Frame 0874. An executed power of attorney and statement pursuant to 37 CFR § 3.73, signed by Nancy M. Cohen, Vice President and Secretary, is attached to this application at Attachment A.

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APP1

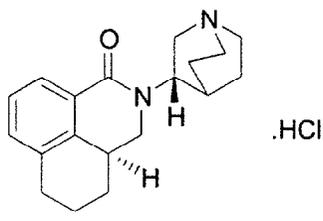
Roche Palo Alto LLC submits this application for extension of the patent term of US Patent No. 5,202,333 by providing the following information, as required by 35 USC 156 and 37 CFR 1.710 *et seq.*

1. Complete identification of product

The approved product is Aloxi™ (palonosetron hydrochloride) injection.

It comprises a compound having:

(a) the structural formula:



(b) the molecular formula:  $C_{19}H_{24}N_2O.HCl$ ;

(c) the molecular weight: 332.87;

(d) the chemical names:

(1) (3a*S*)-2,3,3a,4,5,6-hexahydro-2-[(3*S*)-3-quinuclidinyl]-1*H*-benz[*de*]isoquinolin-1-one  
monohydrochloride

[from the 2003 *USP Dictionary of USAN and International Drug Names*];

(2) 2-(1-azabicyclo[2.2.2]oct-3*S*-yl)-2,3,3a*S*,4,5,6-hexahydro-1*H*-benz[*de*]isoquinolin-1-one  
hydrochloride

[from US Patent No. 5,202,333, e.g. at claim 32]; and

(3) (3a~~S~~)-2-[(~~S~~)-1-Azabicyclo [2,2,2] oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1Hbenz[~~de~~]isoquinoline hydrochloride

[from the proposed labeling for Aloxi™, Attachment H];

(e) the generic names:

palonosetron hydrochloride (USAN) and

palonosetron (INN); and

(f) the CAS registry numbers:

135729-62-3 (palonosetron hydrochloride) and

135729-56-5 (palonosetron).

## 2. Identification of Federal statute/provision of law

Aloxi™ (palonosetron hydrochloride) injection was subject to regulatory review under 21 USC 355(b)(1) [§505(b)(1) of the Federal Food, Drug and Cosmetic Act].

## 3. Date on which product received permission for commercial marketing or use

Aloxi™ (palonosetron hydrochloride) injection received permission for commercial marketing under 21 USC 355(b)(1) on July 25, 2003.

## 4. Identification of active ingredient

Aloxi™ (palonosetron hydrochloride) injection contains as its sole active ingredient palonosetron hydrochloride, described above in item 1. To the best of applicant's knowledge, this product has not previously been approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

**5. Time period for submitting application**

This application for extension of patent term is being submitted within the period permitted for submission under 35 USC 156(d)(1)(A), i.e. the sixty day period beginning on the date the product received permission for commercial marketing. This period began on July 25, 2003 and ends on September 23, 2003.

**6. Identification of patent**

The patent for which patent term extension is being sought is US Patent No. 5,202,333, "Tricyclic 5-HT<sub>3</sub> Receptor Antagonists", inventors Jacob Berger, Robin D. Clark, Richard M. Eglen, William L. Smith, and Klaus K. Weinhardt, which issued on April 13, 1993. The term of US Patent No. 5,202,333 will expire, unless extended, on April 13, 2010, seventeen years from the date on which the patent was issued.

**7. Copy of patent**

A complete copy of US Patent No. 5,202,333, including specification and claims, is attached as Attachment B.

**8. Other patent documents**

The fourth and eighth year maintenance fees have been paid; and copies of the maintenance fee statements (from the Patent & Trademark Office Web site) verifying the payments are attached as Attachment C. The twelfth year maintenance fee may not be paid until April 13, 2004 at the earliest, and may be paid as late as April 13, 2005 with a surcharge.

No disclaimer, Reexamination Certificate, or Certificate of Correction has issued in US Patent No. 5,202,333.

A copy of the Notice of Recordation and assignment from the inventors to Syntex (U.S.A.) Inc. is attached as Attachment D.

A copy of the Notice of Recordation and Certificate of Merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC is attached as Attachment E.

A copy of the Notice of Recordation and Certificate of Amendment changing the name of Syntex (U.S.A.) LLC into Roche Palo Alto LLC is attached as Attachment F.

9. Claims covering the product

US Patent No. 5,202,333 claims Aloxi™ (palonosetron hydrochloride) injection in the following applicable claims:

Claim 1 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of Formula 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R<sup>3</sup> is a group of formula (b) in which u is 0 and z is 2].

Claim 2 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 1 in which both q and u are 0, and p is 0].

Claim 3 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 2 in which p is 0].

Claim 4 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 3 in which R<sup>3</sup> is 1-azabicyclo[2.2.2]oct-3-yl].

Claim 27 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 4 in which the optional double bond is absent].

Claim 29 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 27 in which n is 2].

Claim 30 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of a compound of claim 29 in which R<sup>3</sup> is 1-azabicyclo[2.2.2]oct-3-yl, named as 2-(1-azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one].

Claim 31 covers, *inter alia*, palonosetron hydrochloride [a pharmaceutically acceptable salt of a compound of claim 30 which is 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one].

Claim 32 covers palonosetron hydrochloride [a compound of claim 31 which is 2-(1-azabicyclo[2.2.2]oct-3S-yl)-2,3,3aS,4,5,6-hexahydro-1H-benz[de]isoquinolin-1-one hydrochloride].

Claim 40 covers, *inter alia*, a composition for treating emesis [a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain] comprising a therapeutically effective amount of palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of claim 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R<sup>3</sup> is a group of formula (b) in which u is 0 and z is 2] in combination with a pharmaceutically acceptable carrier.

Claim 41 covers, *inter alia*, a method for treating emesis [a condition chosen from emesis, a gastrointestinal disorder treatable with prokinetic agents, anxiety/depressive state, and pain] in an animal in need of such treatment, comprising administering a therapeutically effective amount of palonosetron hydrochloride [a pharmaceutically acceptable salt of an individual isomer of the compound of claim 1 in which the optional double bond is absent, n is 2, p and q are each 0, and R<sup>3</sup> is a group of formula (b) in which u is 0 and z is 2] to such animal.

Claim 46 covers, *inter alia*, a method for treating emesis in an animal in need of such treatment, comprising administering a therapeutically effective amount of palonosetron hydrochloride to such animal [a method of claim 41 in which the condition is emesis].

Claim 47 covers, *inter alia*, a method for treating emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis, comprising

administering a therapeutically effective amount of palonosetron hydrochloride to such human [a method of claim 46 in which the condition is emesis in humans undergoing cancer treatment with a cytotoxic pharmaceutical agent or radiation at levels sufficient to induce emesis].

10. **Relevant dates and information pursuant to 35 USC 156(g)**

The relevant dates and information under 35 USC 156(g) and 37 CFR 1.740(a)(10)(i) are as follows:

- (A) December 22, 1992: Effective date of IND 39,797;
- (B) September 27, 2002: Submission date of NDA 21-372; and
- (C) July 25, 2003: Approval date of NDA 21-372.

**11. Brief description of significant activities**

A brief description of the significant activities undertaken during the regulatory review period is set forth below in chart form. Please note that IND 39,797 was filed by Syntex (U.S.A.) Inc., the predecessor company to Roche Palo Alto LLC [see the Certificate of Merger of Syntex (U.S.A.) Inc. into Syntex (U.S.A.) LLC in Attachment E and the Certificate of Amendment changing the name of Syntex (U.S.A.) LLC to Roche Palo Alto LLC in Attachment F]. The IND was transferred by Syntex (U.S.A.) Inc. to Helsinn Healthcare SA on August 3, 1998; and NDA 21-372 was submitted by Helsinn Healthcare SA. An authorization from Helsinn Healthcare SA to Roche Palo Alto LLC to rely upon the activities of Helsinn Healthcare SA before the US Food and Drug Administration during the regulatory review period in making its applications for extension of patent term, and granting the Commissioner of Food and Drugs and the Commissioner for Patents the right to refer to IND 39,797 and NDA 21-372 in determining the eligibility of Roche Palo Alto LLC for such extensions, is attached as Attachment G. Helsinn Healthcare SA is licensed under U.S. Patent No. 5,202,333.

Date		Document	Summary
June 6, 1992	IND 39,797	Submission of FDA 1571 Form	Original submission - notice of claimed investigational exemption for intravenous administration of a novel, selective 5-hydroxytryptamine receptor 3 antagonist. RS 25259.
June 18, 1992	IND 39,797	Letter from FDA	Acknowledgement of receipt of new IND submitted and assigning number
July 7, 1992	IND 39,797	Telephone Call from FDA	Notification of clinical hold for IND 39,797.
July 15, 1992	IND 39,797	Letter from FDA	Statement that the proposed study under this IND may not be initiated because of deficiencies. The information is insufficient.
July 31, 1992	IND 39,797	Letter to FDA ( Serial 001)	Partial response to FDA requests for information in the 7/15/92 letter
September 30, 1992	IND 39,797	Letter from FDA	FDA letter from S. Fredd providing list of information needed in order to initiate the clinical study.
October 16, 1992	IND 39,797	Letter from FDA	FDA comments, recommendations and requests re the chemistry portion of the submission.
November 9, 1992	IND 39,797	Letter to FDA ( Serial 002)	Complete response to clinical hold issues. Syntex conducted two additional pre-clinical studies to further elucidate the effects of RS 25259-197 on cardiac conduction and on the autonomic nervous system.
December 22, 1992	IND 39,797		<b>Telephone call from FDA confirming clinical hold is lifted. Effective date of IND application.</b>
January 15, 1993	IND 39,797	Serial 003	Submission of preclinical in vitro study utilizing RS 42358-197 entitled "An In Vitro Assessment of the Cardiotoxic Effects of 5-HT <sub>3</sub> Receptor Antagonists". The results of the abstract suggest that RS 42358 is cytotoxic in an in vitro preparation of rat cardiac myocytes.
January 20, 1993	IND 39,797	Serial 004 (Protocol Amendment)	New Protocol and Investigators for study <u>RGR 2092</u> entitled "A Single Ascending Dose Safety and Pharmacokinetics Study of IV RS25259 in Healthy Volunteers".
January 22, 1993		Amendment # 005	Submitting to FDA a report supporting a change

	IND 39,797	(Chemistry/Microbiology)	in the packaging container for RS 25259 IV Solution.
March 15, 1993	IND 39,797	Amendment # 007 (Chemistry/Microbiology)	Information Amendment: Submission of changes to the synthetic scheme
April 28, 1993	IND 39,797	Amendment # 010 (Protocol Amendment)	Change in the Protocol for study RGR 2092
June 1, 1993	IND 39,797	Amendment # 011 (Protocol Amendment)	New Protocol for study RFR 2216 entitled "Plasma, Pharmacokinetics, Metabolism and Excretion IV[14C]197 After Intravenous Injection"
July 21, 1993	IND 39,797	Amendment # 015 (Protocol Amendment)	Change in Protocol for study RGR 2092 .
August 6, 1993	IND 39,797	Amendment # 016	ANNUAL REPORT (June 3, 1992 - March 2, 1993)
October 4, 1993	IND 39,797	Amendment # 018 (Protocol Amendment)	New Protocol and Investigators for study RGR/259s2120/USA entitled: "A Safety, Antiemetic Efficacy and Pharmacokinetic Study of Single dose IV RS25259-197 in Cisplatin-Naïve Cancer Patients Receiving High-Dose Cisplatin Chemotherapy".
November 19, 1993	IND 39,797	Amendment # 020 (Protocol Amendment)	New Clinical Investigator for study RGR/259s2120/USA.
December 23, 1993	IND 39,797	Amendment # 021 (Protocol Amendment)	Change in Protocol: for study 2120. Referencing FDA letter 11/2/93. Response to Division comments.
February 4, 1994	IND 39,797	Amendment # 022 (Pharmacology/Toxicology)	Information Amendment: Report AT 6161.
February 11, 1994	IND 39,797	Amendment # 023 (Chemistry/Microbiology)	Information Amendment: Synthesis route changed .
February 14, 1994	IND 39,797	Amendment # 024 (Protocol Amendment)	New Protocol and Investigators for study 25259s2500 entitled "A Dose Ranging Safety and Efficacy Comparison of Four Dose Levels of Intravenous RS-25259 to Placebo in the Prevention of Postoperative Nausea and Vomiting Following Abdominal and Vaginal Hysterectomy".
March 4, 1994	IND 39,797	Amendment # 025	New Investigator for study 25259s2500
March 24, 1994	IND 39,797	Amendment # 026 (Protocol Amendment)	New Protocol and Investigator for study 25259s2330 entitled "A Dose Ranging Efficacy, Safety and Pharmacokinetic Study of Single Intravenous Doses of RS25259 for Prevention of Nausea and Vomiting in Chemotherapy-Naïve Cancer Patients Receiving Highly Emetogenic Chemotherapy".
April 6, 1994	IND 39,797	Amendment # 027 (Protocol Amendment)	New Investigator for study 25259s2500 New Investigator for study 25259s2330
May 5, 1994	IND 39,797	Amendment # 028 (Protocol Amendment)	New Investigator for study 25259s2500

June 1, 1994	IND 39,797	Amendment # 029 (Protocol Amendment)	New Investigator for study 25259s2330 New Investigator for study 25259s2500 Information Amendment: Pharmacology / Toxicology: Databank Report AT 6664.
June 1, 1994	IND 39,797	Amendment # 030 (Pharmacology/Toxicology)	Information Amendment: final report AT 6655. Other: Draft protocol. Proposed 2 year protocol entitled "Oral Gavage Carcinogenicity Study with RS 25259-197 in Rats".
June 27, 1994	IND 39,797	Amendment # 031 (Protocol Amendment)	Change in Protocol for study 25259s2330
July 5, 1994	IND 39,797	Amendment # 032	Information Amendments Chemistry /Microbiology: Changes to CMC re: batch PA 17555-103 of RS25259-197. Pharmacology /Toxicology: final report filed to this IND and cross referenced to IND 42,886/018 CL 6721. Final report AT 6664 supercedes final report AT 6000. Clinical: additional clinical study site for study 25259s2330. New Investigator for study 25259s2330 .
July 22, 1994	IND 39,797	Amendment # 033	ANNUAL REPORT (March 3, 1993 – March 2, 1994)
August 2, 1994	IND 39,797	Amendment # 034 (Chemistry/Microbiology)	Information Amendment: Alternate route synthesis for RS 25259-197, lot PA 17555-103 and lot PA 17555-53.
August 5, 1994	IND 39,797	Amendment # 035	Information Amendment (Clinical): New name of clinical site. New Investigator for study 25259s2330. New Investigator for study 25259s2500 Pharmacology /Toxicology: preclinical report filed to IND 42,886/021 and cross reference to this IND AT 6700.
August 15, 1994	IND 39,797	Amendment # 036 (Protocol Amendment)	Change in Protocol for study 25259s2500 Change in Protocol for study 25259s2330
September 5, 1994	IND 39,797	Amendment # 037	Chemistry /Microbiology: annual stability statement for RS25259-197 IV Solution. Clinical: clinical laboratory update for protocol 25259s2330; New Investigator for study 25259s2330
October 6, 1994	IND 39,797	Amendment # 038	New Investigator for study 25259s2330  Pharmacology /Toxicology: preclinical report filed to this IND. AT 6750 & AT 6751.
October 14, 1994	IND 39,797	Amendment # 039	Proposed carcinogenicity protocol.
November 1, 1994	IND 39,797	Letter from FDA	Letter to M. Reitman from S. Fredd re: comments and recommendations re: 3-months dose ranging study and carcinogenicity study protocol.
November 9, 1994	IND 39,797	Amendment # 040 (Information and Protocol Amendments)	New Investigator for study 25259s2330 Chemistry /Microbiology: letter detailing additional manufacturing site, including analytical

			test results, synthetic description and scheme and stability statement. Pharmacology /Toxicology: preclinical reports AT 6777, AT 6755 & AT 6756.
December 5, 1994	IND 39,797	Amendment # 041 (Protocol Amendment)	New Investigator for study 25259s2330
December 7, 1994	IND 39,797	Amendment # 042	Safety Report Study 25259s2332,
January 6, 1995	IND 39,797	Amendment # 043 (Pharmacology/Toxicology)	Information Amendment: final preclinical report filed to IND 42,886/028 and cross referenced to this IND. AT 6787.
February 6, 1995	IND 39,797	Amendment # 044 (Protocol Amendment)	New Investigator for study 25259s2300
February 23, 1995	IND 39,797	Amendment # 045 (Clinical)	Information Amendment: final clinical report filled to this IND. CL 6951.
March 6, 1995	IND 39,797	Amendment # 046 (Protocol Amendment)	New Investigator for study 25259s2330 Information Amendment (Clinical): addition of clinical lab and/or research facilities.
March 14, 1995	IND 39,797	Letter from FDA	Letter to G. Rouleux from S. Fredd re: mouse carcinogenicity study comments.
April 10, 1995	IND 39,797	Amendment # 047 (Protocol Amendment)	New Investigator for study 25259s2330 Information Amendment (Clinical): Addition of clinical laboratory facility to be used in study 25259s2330.
September 25, 1995	IND 39,797	Amendment # 049 (Chemistry/Microbiology)	Information Amendment re: Stability statement of drug substance stability and analytical method. Other: Notification of new clinical/safety monitor, K. Friday.
May 24, 1996	IND 39,797	Amendment # 050 (Pharmacology/Toxicology)	Information Amendment: Preclinical reports submitted in full to the IND for the first time: AT 6824 AT 6976
August 1, 1996	IND 39,797	Amendment # 051	ANNUAL REPORT (March 3, 1995 through March 2, 1996)
July 31, 1997	IND 39,797	Amendment # 052	ANNUAL REPORT (March 3, 1996 through March 2, 1997)
July 23, 1998	IND 39,797	Amendment # 053	ANNUAL REPORT (March 3, 1997 through March 2, 1998)
July 31, 1998	IND 39,797	Amendment # 054	Transfer of Ownership from Syntex (U.S.A.) Inc. to Helsinn SA.
August 3, 1998	IND 39,797	Amendment # 055	Transfer of Syntex IND 39,797 (RS-25259-197, Palonosetron) to Helsinn Healthcare SA.
September 29, 1998	IND 39,797	Telephone to Kati Johnson	IND 39,797 program input; end of phase 2 meeting information. IND 42,886 program status.
November 12, 1998	IND 39,797	Amendment # 056	Preclinical program background package.
December 23, 1998	IND 39,797	Amendment # 057	Request for End of Phase 2 meeting.
January 19, 1999	IND 39,797	Fax from FDA	EOP2 meeting scheduled for March 15, 1999.
January 27, 1999	IND 39,797	Amendment # 058	Preclinical program background package; information to Amendment # 56.
February 1, 1999	IND 39,797	Letter from FDA	Request for further information to complete change of sponsorship (Serials # 54 and # 55).

February 5, 1999	IND 39,797	Fax from FDA	EOP2 meeting scheduled for March 10.
February 15, 1999	IND 39,797	Amendment # 059	Background Document for March 10, 1999 End of Phase 2 meeting.
March 2, 1999	IND 39,797	Telephone from Ms. McNeil	Studies 2500 and 2502 efficacy results
March 4, 1999	IND 39,797	Fax to FDA	Desk copy of studies 2500 and 2502.
March 8, 1999	IND 39,797	Telephone to Dr. Goldkind	Reviewer comments.
March 19, 1999	IND 39,797	Meeting	End-of-Phase 2 Meeting with FDA.
March 29, 1999	IND 39,797	Amendment # 60	Reply to FDA letter of February 1, 1999 about the change of Sponsorship.
April 29, 1999	IND 39,797	Letter from FDA	FDA comments and recommendations referred to amendments # 56 and # 58 and the EOP2
May 7, 1999	IND 39,797	Amendment # 062	Revised study termination report-Syntex carcinogenicity study in mice; Cross-reference to IND 42,886 Palonosteron Hydrochloride Oral.
May 21, 1999	IND 39,797	Letter from FDA	EOP2 biopharmaceutics conference call meeting minutes.
August 19, 1999	IND 39,797	Amendment # 064	Phase 3 and Commercial Formulation.
September 24, 1999	IND 39,797	Amendment # 065	Annual Report.
October 15, 1999	IND 39,797	Amendment # 066	PALO 99-08, CLE 1063/1 "Palonosteron Hydrochloride: 26 Week Intravenous Administration Toxicity Study in the Rat with a 4 Week intravenous-free Period". IND Safety Report: Initial Written report.
November 24, 1999	IND 39,797	Amendment # 068	Phase 3 efficacy protocol PALO 99-03. Request for Special Protocol Assessment and Agreement.
November 24, 1999	IND 39,797	Amendment # 069	Phase 3 efficacy protocol PALO 99-04. Request for Special Protocol Assessment and Agreement.
November 30, 1999	IND 39,797	Amendment # 070	Toxicology study PALO-99-08; CLE-1063/1 Information Amendment: Follow-up and Additional Information to IND Safety Report, IND Amendment # 66.
December 10, 1999	IND 39,797	Amendment # 071	Phase 3 efficacy protocol PALO 99-05. Request for Special Protocol Assessment and Agreement.
December 22, 1999	IND 39,797	Amendment # 072 (Protocol Amendment)	New protocol, PALO 99-39 Phase 1 ADME study.
April 7, 2000	IND 39,797	Amendment # 074 (Protocol Amendment)	New Protocols, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05.
April 24, 2000	IND 39,797	Amendment # 075	Proposed Pediatric Study Request (PPSR).
April 26, 2000	IND 39,797	Amendment # 076	Phase 3 efficacy protocol PALO 00-01. Request for Special Protocol Assessment and Agreement.
May 22, 2000	IND 39,797	Amendment # 077 (Protocol Amendment)	New protocol, Phase 3 Protocol PALO-99-06.
June 5, 2000	IND 39,797	Amendment # 078	Request for teleconference with Pharm/Tox Reviewer to Discuss Segment 3 Reprotox Study.
June 9, 2000	IND 39,797	Letter from FDA	FDA response to the PALO-00-01 FDAMA special protocol review request.

June 14, 2000	IND 39,797	Letter from FDA	Reply to June 5 and 6, 2000 correspondence requesting a meeting to discuss the acceptability of a completed Segment 3 pre- and post-natal study of palonosetron in rats.
June 19, 2000	IND 39,797	Amendment # 079 (Protocol Amendment)	New Investigators, Phase 3 protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO-99-06.
June 30, 2000	IND 39,797	Amendment # 080	IND Safety Report-In-Vitro Purkinje Fiber Dog Data.
July 19, 2000	IND 39,797	Amendment # 081 (Protocol Amendment)	New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO-99-06.
August 4, 2000	IND 39,797	Amendment # 082	Follow up to IND Safety Report - In Vitro Purkinje Fiber Dog Data (IND Amendment # 80, submitted June 30, 2000).
August 9, 2000	IND 39,797	Letter from FDA	FDA reply to amendment dated June 30, 2000 (serial # 80).
August 14, 2000	IND 39,797	Amendment # 083 (Protocol Amendment)	New protocol, Pediatric Protocol PALO-99-07.
August 17, 2000	IND 39,797	Telephone to Melodi McNeil	Dr. Talarico's letter (received today) dated August 9, 2000, regarding our original plans to exclude patients from phase 3 trials who are taking comeds which prolong QTC.
August 18, 2000	IND 39,797	Amendment # 084 (Protocol Amendment)	New investigators, Phase 3 Protocols PALO-99-04, PALO-99-05, PALO-99-06.
August 24, 2000	IND 39,797	Amendment # 085 (information Amendment)	Chronic Toxicology Draft Reports for Palonosetron, 9-month in Dog, 26-week in Rat.
August 24, 2000	IND 39,797	Amendment # 086	New Protocols, Phase 1 protocols PALO-99-35 and PALO-99-51.
August 24, 2000	IND 39,797	Telephone to Melodi McNeil	Serial # 82 Follow-up to Safety Report (Serial # 80), plan to allow comeds which prolong QTC in Phase 3 Trials.
August 29, 2000	IND 39,797	Amendment # 087	Phase 1 protocols PALO-99-35 and PALO-99-51.
September 8, 2000	IND 39,797	Amendment # 088 (Information Amendment)	ReproTox Final Reports for Palonosetron.
September 20, 2000	IND 39,797	Amendment # 090	New Investigators PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06. Change in Protocols, Protocol Amendment No. 2 for PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
September 26, 2000	IND 39,797	Amendment # 091 (Protocol Amendment)	New Investigators PALO-99-03, PALO-99-05, PALO-99-06, and PALO-99-07.
September 26, 2000	IND 39,797	Letter from FDA	FDA reply to Pediatric Study Request PALO-99-07.
September 28, 2000	IND 39,797	Amendment # 092	IND Annual Report.
October 16, 2000	IND 39,797	Amendment # 093 (Information Amendment)	Rat Carcinogenicity Study PALO-98-03, Decreasing Number of Survivors in High Dose Female Group - Request for Guidance. Cross-

			reference to IND 42,886, Palonosetron Hydrochloride Oral.
November 6, 2000	IND 39,797	Fax to Melodi McNeil (2)	Serial #93, October 16, 2000 – Request for confirmation of Dr. Choudary's feedback of October 17, 2000 regarding the loss rate in the high dose female group in the Palonosetron Rat Carcinogenicity Study.
November 14, 2000	IND 39,797	Letter from Dr. Talarico	FDA letter from Dr. Talarico (undated and unsigned) postmarked 9 Nov 2000 – FDA evaluation of juvenile rat and dog tox studies, follow-up FDA requests, and FDA request for full reports and data for dog in-vitro and in-vivo CVS studies.
November 17, 2000	IND 39,797	Amendment # 094 (Protocol Amendment)	New Investigators, PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
November 22, 2000	IND 39,797	Amendment # 095 (Request for teleconference)	Request for teleconference to discuss the proposed NDA CMC strategy.
November 30, 2000	IND 39,797	Amendment # 096 (Request for teleconference)	Request for Teleconference to Discuss the Proposed Pediatric Protocol PALO-99-07.
December 12, 2000	IND 39,797	Amendment # 097 (Response to FDA request for information)	Reply to FDA Letter Postmarked November 9, 2000, Regarding the 28-Day Juvenile Rat and Dog Studies and the <i>in vivo</i> Dog Cardiovascular Safety Study.
December 15, 2000	IND 39,797	Fax from FDA	FDA fax confirmation of CMC Strategy teleconference of Jan 30, 2001
December 18, 2000	IND 39,797	Amendment # 098 (Protocol Amendment)	New Protocol, Phase 1 Protocol PALO-99-34.
December 20, 2000	IND 39,797	Amendment # 099 (Protocol Amendment)	New Investigators, PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
December 26, 2000	IND 39,797	Fax from FDA	FDA fax confirming (1) Pediatric protocol teleconference February 8, 2001, and (2) CMC Strategy meeting January 30 <sup>th</sup> instead of a teleconference.
January 2, 2001	IND 39,797	Amendment # 100	Protocol Amendment, Change in Protocols, Protocol Amendment No. 3 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
January 25, 2001	IND 39,797	Amendment # 103 (New Investigators)	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05 and PALO-99-06.
January 30, 2001	IND 39,797	Meeting	CMC strategy meeting with FDA.
January 31, 2001	IND 39,797	Letter from Dr. Talarico	FDA letter from Dr. Talarico dated 31 Jan 2001 (in electronic signature page) regarding juvenile rat tox data – FDA recommendation that –07 patients be evaluated for ophthalmic function.

February 8, 2001	IND 39,797	Telephone to Melodi McNeil	FDA agreement with Helsinn's replies (submitted in IND Serial #96) to FDA's comments and request (FDA letter, 26 Sept 2000) regarding the PALO-99-07 pediatric protocol, and agreement to cancel the FDA/Helsinn Pediatric Protocol teleconference scheduled for 8 Feb 2001.
February 22, 2001	IND 39,797	Telephone to Melodi McNeil	Resuming treatment in the high dose female group, in the Palonosetron rat carcinogenicity study until 20% of the group (n=13) remains as survivors, then discontinue treatment, do not kill the animals, and allow the group to proceed to the end of the 104 week study.
February 23, 2001	IND 39,797	Telephone to Melodi McNeil	Resumption of treatment administration to high dose female rats in the PALO-98-03 rat carcinogenicity study.
February 27, 2001	IND 39,797	Letter from FDA	FDA minutes of Palonosetron NDA CMC strategy meeting held January 30, 2001.
March 8, 2001	IND 39,797	Letter from FDA	FDA letter electronically dated 8 March, 2001 re: FDA's response to our replies of 30 November 2000 (Serial # 96) regarding the pediatric PALO-99-07 protocol.
April 9, 2001	IND 39,797	Telephone to Peggy Hair	Issuance of Palonosetron NDA Number - NDA 21-372.
April 10, 2001	IND 39,797	Amendment # 106 (Pharmacology / Toxicology)	Mouse Carcinogenicity Study PALO-99-18, Decreasing Number of Survivors in Intermediate Dose Female Group - Request for Guidance.
April 10, 2001	IND 39,797	Amendment # 107 (Change in protocol)	Protocol Amendment, Change in protocols, protocol Amendment No. 4 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
April 13, 2001	IND 39,797	Telephone from Melodi McNeil	IND Serial # 106, 10 april 2001, 20 survivors in intermediate female dose group, mouse carcinogenicity study.
April 17, 2001	IND 39,797	Amendment # 108 (Pharmacology / Toxicology)	Information Amendment: Rat carcinogenicity study PALO-98-03, notification of N=13 survivors in high dose female group, request for confirmation to discontinue treatment of this group only.
April 19, 2001	IND 39,797	Amendment # 109 (Clinical)	Information Amendment: IV Dexamethasone Shortage in the US-Request for preliminary FDA Feedback regarding the acceptability using alternative corticosteroid comeds in Phase 3 efficacy Protocol PALO-99-05.
May 30, 2001	IND 39,797	Amendment # 112 (Pharmacology / Toxicology) (Clinical)	Reply to FDA Letter electronically dated 31 January 2001, Regarding the 28-Day Juvenile Rat Study PALO-99-12 and Pediatric Clinical Trial PALO-99-07.
June 19, 2001		Telephone to/from Melodi McNeil	1) Status of FDA feedback re IND Serial # 107 (Protocol Amendment # 4 to PALO-99-03,

	IND 39,797		PALO-99-04, PALO-99-05, and PALO-99-06), 2) Status of FDA feedback re IND Serial # 109 (IV Dexamethasone shortage in the US- alternatives for use in PALO-99-05).
June 25, 2001	IND 39,797	Letter from Dr. L. Talarico	FDA formal acceptance of dex alternative for PALO-99-05.
July 23, 2001	IND 39,797	Amendment # 114 Chemistry, Manufacturing and Controls	New Site (Helsinn Advanced Synthesis ) for Drug Substance Manufacture. New Site (SP Pharmaceuticals) for Manufacture of Phase 3 Clinical Supplies. 18-Month Stability for Phase 3 Clinical Supplies manufactured by Oread.
July 30, 2001	IND 39,797	Amendment # 115	Protocol Amendment, Change in Protocols, Protocol Amendment No.5 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO- 99-05, and PALO-99-06. Request for Change in Documented Special Protocol Assessments.
August 1, 2001	IND 39,797	Amendment # 116	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO- 99-05, and PALO-99-06.
August 2, 2001	IND 39,797	Telephone to/from Mr. Brian Strongin	(1) Mr. Brian Strongin, newly appointed FDA Project Manager for the Palonosetron INDs (2) 45-day clock for Special Protocol Review of Serial # 115, Protocol Amendment # 5 to PALO- 99-03, PALO-99-04, and PALO-99-05.
August 2, 2001	IND 39,797	Amendment # 117	Telephone (faxed) Safety Report - Anaphylactic Reaction, Patient # 1211 in phase 3 trial PALO- 99-06 (open label safety study).
August 3, 2001	IND 39,797	Letter from Dr. L. Talarico	FDA letters received re: Serial # 107 (Protocol Amendment # 4).
August 3, 2001	IND 39,797	Letter from Mr. Brian Strongin	Acknowledgement of receipt of Amendment Serial # 115 (Protocol Amendment # 5) to PALO-99-03, PALO-99-04 and PALO-99-05.
August 14, 2001	IND 39,797	Telephone to Mr. Brian Strongin	Notification of pending correction to protocol amendment # 5 to PALO-99-03, PALO-99-04, PALO-99-05 and PALO-99-06.
August 23, 2001	IND 39,797	Amendment # 118	Protocol Amendment, Change in Protocols, Correction to Protocol Amendments No. 5 to Phase 3 Clinical Protocols PALO-99-03, PALO- 99-04, PALO-99-05, and PALO-99-06. Request for Change in Documented Special Protocol Assessment.
August 23, 2001	IND 39,797	Amendment # 119	IND Safety Report - Acute Psychosis, Patient # 3454 in Phase 3 trial PALO-99-03.
August 24, 2001	IND 39,797	Amendment # 120	Information Amendment - Pharmacology: Summary Review and Reports of Palonosetron Pre-clinical Cardiovascular Safety (CVS) Studies.
August 27, 2001	IND 39,797	Amendment # 121	Request for Meeting to Review and Discuss the Palonosetron Pre-clinical Cardiovascular Safety (CVS) Program.
August 28, 2001	IND 39,797	Letter from Mr. Brian Strongin	FDA letter re receipt of Serial # 118, Protocol Amendment # 5 resubmission for Protocols

			PALO-99-03, PALO-99-04, and PALO-99-05.
September 6, 2001	IND 39,797	Amendment # 122	Request for teleconference to clarify FDA <u>statistical</u> feedback in FDA Special Protocol Assessment reply letters dated January 10, 2000, January 10, 2000, and January 27, 2000, respectively, regarding phase 3 efficacy protocols PALO-99-03, PALO-99-04, and PALO-99-05.
September 19, 2001	IND 39,797	Amendment # 123	Information Amendment: Pharmacology-Toxicology, Final Report PALO-00-19, Entitled, "Palonosetron Hydrochloride: ECG measurements from 28 Day Intravenous Administration Toxicity Study (PALO-99-22; Covance Study Number 1063/17) in the Juvenile Dog".
September 20, 2001	IND 39,797	Amendment # 124	Follow-up to IND Safety Report, Serial # 80, June 30, 2000. Retrospective Evaluation of ECG Tracing Collected During the Phase I and II Development of Palonosetron: Cardiovascular Safety Profile.
September 28, 2001	IND 39,797	Amendment # 125	Request for Pre-NDA Meeting.
October 3, 2001	IND 39,797	Amendment # 126	2001 IND Annual Report.
October 5, 2001	IND 39,797	Letter to Mr. Brian Strongin	Additional desk copies of Serial # 121 for FDA CVS teleconference on November 8, 2001, 1:00 - 2:30 PM.
October 5, 2001	IND 39,797	Letter from Mr. Victor Raczkowski	FDA letter, dated 5 October 2001, re review of submission # 118 (Phase 3 Protocol Amendment # 5).
October 10, 2001	IND 39,797	Amendment # 128	Request for Clinical Pharmacology and Biopharmaceutics Teleconference to Discuss Phase 3 Palonosetron Population PK/PD Protocol PALO-99-33.
October 10, 2001	IND 39,797	Letter from Mr. Victor Raczkowski	Letter from FDA re Request for pre-NDA meeting.
October 15, 2001	IND 39,797	Amendment # 129	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06.
October 18, 2001	IND 39,797	Fax from FDA / Mr. Brian Strongin	Fax from FDA re statistical teleconference.
October 29, 2001	IND 39,797	Fax from Ms. Helen Wilson	Fax from FDA re Nov. 30, 2001 10-11 AM EST Pop PK/PD teleconference.
November 2, 2001	IND 39,797	Letter from Mr. Brian Strongin	Minutes from the October 18 <sup>th</sup> teleconference.
November 6, 2001	IND 39,797	Telephone to Mr. Brian Strongin	Status of Dr. Choudary's replies to our questions submitted in Serial # 122 (30 May 2001) regarding the juvenile rat tox report.
November 6, 2001	IND 39,797	Telephone to Mr. Hugo Gallo-Torres	Re: Communication Record re Serial # 124, Assessment of Phase 1 and 2 ECGs.
November 21, 2001	IND 39,797	Amendment # 130	IND Safety Report - Rat Carcinogenicity Data.

November 21, 2001	IND 39,797	Fax to Mr. Brian Strongin	Re: Status of Palonosetron Biopharmaceutics Program as requested by FDA in preparation for the upcoming population PK/PD teleconference scheduled for November 30, 2001.
November 27, 2001	IND 39,797	Fax from Mr. Brian Strongin	Teleconference regarding Palo-99-33 Protocol. Responses to HHC's questions.
December 4, 2001	IND 39,797	Fax from Mr. Brian Strongin	Response to Questions Regarding the Interconversion Study.
December 10, 2001	IND 39,797	Amendment # 131	Reply to FDA Minutes, and Sponsor's Minutes, FDA Statistical Teleconference held October 18, 2001 in follow-up to the Special Protocol Assessments.
December 11, 2001	IND 39,797	Amendment # 132	Protocol Amendment, Change in Protocols, Protocol Amendment # 6 to Phase 3 Clinical Protocols PALO-99-04 and PALO-99-05. Request for Change in Documented Special Protocol Assessments.
December 17, 2001	IND 39,797	Fax from Mr. Brian Strongin	FDA Minutes, preclinical CVS meeting held on 8 November 2001.
December 17, 2001	IND 39,797	Amendment # 133	Notification to FDA of discontinuation of an investigator from IND clinical trials.
December 26, 2001	IND 39,797	Letter from FDA	Officials minutes, meeting held on November 30, 2001.
January 8, 2002	IND 39,797	Amendment # 134	Sponsor's Minutes, FDA Pop PK/PD Teleconference held November 30, 2001.
January 8, 2002	IND 39,797	Amendment # 135	Sponsor's Minutes, Preclinical Cardiovascular Safety Teleconference held November 8, 2001.
January 8, 2002	IND 39,797	Amendment # 136	Information Amendment - Reply to FDA Letter Dated August 3, 2001.
January 11, 2002	IND 39,797	Amendment # 137	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-04, PALO-99-05, and PALO-99-06.
January 16, 2002	IND 39,797	Amendment # 138	Reply to FDA's phoned questions of January 14, 2002, regarding Protocol Amendment # 6 to PALO-99-04 and PALO-99-05 (Serial # 132 dated December 11, 2001).
January 17, 2002	IND 39,797	Telephone to Mr. Kairy Malek	FDA request for Palonosetron protocols and all protocol amendments, plus monitoring reports for all Palonosetron studies performed at Dr. Kovacs site.
January 24, 2002	IND 39,797	Letter from FDA	FDA letter dated 24 <sup>th</sup> January 2002 re: FDA minutes, Palonosetron Stats teleconference held with FDA 18 <sup>th</sup> October, 2001.
January 24, 2002	IND 39,797	Letter from FDA	FDA Special Protocol Assessment letter concerning Protocol Amendment # 6 for PALO-99-04 and PALO-99-05.
January 24, 2002	IND 39,797	Letter from FDA	FDA minutes of stats teleconference held 18 <sup>th</sup> October, 2001.
January 28, 2002	IND 39,797	Letter from FDA	FDA letter dated 28 <sup>th</sup> January, Re: Juvenile rat toxicology study-FDA feedback.

January 29, 2002	IND 39,797	Amendment # 139	Information Amendment - Plans to Perform Additional Pre-Clinical Cardiovascular Safety (CVS) Studies.
February 7, 2002	IND 39,797	Amendment # 140	Request for Pre-NDA Meeting.
February 12, 2002	IND 39,797	Amendment # 141	Protocol, protocol amendments and monitoring-related documents associated with Dr. Kovacs's site.
February 21, 2002	IND 39,797	Amendment # 142	Reply and request, Dr. Raczowski's letter dated 28 January, 2002 regarding 28-day juvenile rat tox study, and ophthalmic function tests in pediatric protocol PALO-99-07.
February 22, 2002	IND 39,797	Fax from Ms. Helen Wilson/FDA	Fax from Ms. Helen Wilson/FDA confirming 10 April 2002 Meeting.
February 28, 2002	IND 39,797	Telephone from Mr. Brian Strongin	FDA feedback regarding timing of ophthalmic exams in PALO-99-07 as requested in Serial # 142.
March 13, 2002	IND 39,797	Amendment # 143	Pre-NDA Meeting Background Package.
March 19, 2002	IND 39,797	Amendment # 144	Labeling information as supplement to IND Serial # 114, SP Pharmaceuticals providing clinical supplies for the phase 3 studies.
March 28, 2002	IND 39,797	Amendment # 145	Protocol Amendment; PALO-99-35 and PALO-99-51
April 1, 2002	IND 39,797	Amendment # 146	Phase 3 Clinical Protocol Amendments: Amendment # 6 to PALO-99-03 and Amendment # 7 to PALO-99-04 and PALO-99-05.
April 2, 2002	IND 39,797	Amendment # 147	Information Amendment: Mouse Carcinogenicity Study PALO-99-18 Final Report.
April 3, 2002	IND 39,797	Amendment # 148	Preliminary Efficacy Data for Pivotal Efficacy Study PALO-99-05 involving highly emetogenic CINV.
April 5, 2002	IND 39,797	Amendment # 149	Request for FDA Review of Proposed Proprietary Names for Palonosetron HCl Intravenous Injection.
April 5, 2002	IND 39,797	Amendment # 150	Follow - up, IND Safety Report Serial # 130 - Final Report, Rat Carcinogenicity Study PALO-98-03. Information Amendment: Submission of (1) PALO-99-38 Final Report, Palonosetron: Unscheduled NDA Synthesis in Rat liver Cells <i>In Vivo</i> , (2) PALO-01-16, Summary Results of Chromosomal Aberration Study.
April 8, 2002	IND 39,797	Fax from Mr. Brian Strongin	Responses to questions for the preNDA

			meeting.
April 8, 2002	IND 39,797	Letter from Mr. Victor Raczkowski	Letter from Mr. Victor Raczkowski recommending submission of full reports of PALO-98-03/HS001 and PALO-98-03/HSH002.
April 10, 2002	IND 39,797	Meeting	Pre-NDA Meeting with FDA.
April 22, 2002	IND 39,797	Fax from Mr. Brian Strongin	Request Regarding the Mouse and Rat Carcinogenicity Study Reports Submitted April 2 and April 5, 2002.
April 30, 2002	IND 39,797	Fax to Mr. Brian Strongin	Reply to FDA Request Regarding Mouse and Rat Carcinogenicity Study Reports Submitted April 2 and April 5, 2002 – Identification and Abbreviations in the Reports.
April 30, 2002	IND 39,797	FDA Minutes	FDA Minutes, pre NDA meeting held April 10, 2002.
May 3, 2002	IND 39,797	Amendment # 153	Request for FDA feedback regarding use of the D15 color test in pediatric study PALO-99-07.
May 9, 2002	IND 39,797	Fax to Mr. Brian Strongin	Request for clarification of FM-28 and FM-40 color tests recommended by FDA on 6 May 2002 for use in the PALO-99-07 pediatric trial.
May 20, 2002	IND 39,797	Amendment # 154	Reply to FDA Minutes, Pre-NDA Meeting held April 10, 2002.
May 23, 2002	IND 39,797	Amendment # 155	Sponsor's Minutes, PreNDA Meeting held April 10, 2002.
June 7, 2002	IND 39,797	Fax to Mr. Brian Strongin	Re.: Proposal to submit electronic case report tabulation (CRTs) on CD in the planned Palonosetron NDA.
July 3, 2002	IND 39,797	Fax from Ms. Tawni Schwemer	FDA User's Fees in fiscal year (FY) 2003 (i.e., effective Oct. 1, 2002).
July 24, 2002	IND 39,797	Amendment # 156	Protocol Amendment, New Protocol and Protocol Amendment # 1, Pediatric Protocol PALO-99-07.
September 10, 2002	NDA 21-372	E-mail to Jones / FDA	Helsinn Healthcare SA / User Fee Identification Number: 4391; NDA number 21-732.
September 20, 2002	IND 39,797	Letter from FDA	Status of DMETS review of proposed proprietary name, ALOXI, CINVEX, and

			ONICIT.
September 27, 2002	IND 39,797	Telephone to Mr. Brian Strongin	IND Annual Report, 2002.
September 27, 2002	NDA 21-372	Fax from Chris Celeste	<b>Submission of NDA 21-372 acknowledged by FDA.</b>
October 11, 2002	NDA 21-372	Amendment # 001	Palonosetron Hydrochloride Intravenous Injection, 0.25 mg Amendment # 001.
October 15, 2002	NDA 21-372	Fax to Mr. Brian Strongin	Confirmation of NDA Amendment Submission Addresses Palonosetron NDA 21-372.
October 18, 2002	IND 39,797	Fax from Mr. Brian Strongin	DMETS reviews of the three proposed tradenames for Palonosetron.
November 5, 2002	IND 39,797	Amendment # 157 2002 IND Annual Report	2002 IND Annual Report.
November 7, 2002	NDA 21-372	Letter from Mr. Brian Strongin	FDA letter acknowledging FDA receipt of NDA 21-372.
November 18/19, 2002	NDA 21-372	Telephone from Ele Ibarra-Pratt	Palonosetron clinical study site inspections. information and documentation requested by FDA in preparation for site visits at sites 044 (Ger.), 221 (Russ.) and 212 (Russ.).
November 21, 2002	NDA 21-372	Amendment # 002	Chemistry, Manufacturing and Controls: Letter of Clarification for Helsinn Birex Pharmaceuticals Ltd. To Release Final Product to Commercial Market.
November 26, 2002	NDA 21-372	Telephone from Mr. Brian Strongin	FDA confirmation that Palo NDA has been filed.
November 26, 2002	NDA 21-372	Amendment # 003	Statistical Reviewer Copies of Palonosetron Original NDA Volumes Regarding Rat and Mouse Carcinogenicity Studies.
November 27, 2002	NDA 21-372	Telephone to Ms.Ibarra-Pratt	Site documentation requested by FDA Site # 044 in Germany.
December 2, 2002	NDA 21-372	Fax to Ms.Ibarra-Pratt	Examples of information requested for Palo FDA clinical site inspections in Russia and Germany.
December 9, 2002	NDA 21-372	Telephone to/from Ms.Ibarra-Pratt	FDA request for sponsor representative contact information (not site personnel) near sites # 044, # 212, and # 221 in Germany and Russia for FDA inspectors to contact during inspection of these sites.

December 10, 2002	NDA 21-372	Telephone from Ms. Ibarra-Pratt	Request for site information, US site # 501, Dr. Julio Hajdenberg, New Ritchie, Florida, PALO-99-04 and PALO-99-05 information requested in preparation for FDA site inspection.
December 19, 2002	IND 39,797	Amendment # 158	Pediatric Protocol Amendment: New Investigators for PALO-99-07.
January 14, 2003	NDA 21-372	Fax to Mr. Brian Strongin	Planned four-month safety update for Palonosetron NDA 21-372.
January 20, 2003	IND 39,797	Amendment # 160	Protocol amendment # 2, pediatric protocol PALO-99-07 Information amendment: toxicology, final reports for juvenile rat toxicology study PALO-02-05 and juvenile/neonatal dog toxicology study PALO-99-22.
January 24, 2003	NDA 21-372	Amendment # 004	Four-Month Safety Update.
January 27, 2003	NDA 21-372	Telephone to Ms. Irizarry	Labeling required by FDA for import of DS from HAS (Switzerland) to SP Pharmaceuticals (Albuquerque) for purposes of manufacturing DP validation batches during FDA review (before FDA approval of Palo NDA 21-372.
January 31, 2003	IND 39,797	Telephone from Mr. Brian Strongin	Status of FDA review/ reply to sponsor's request for FDA feedback regarding the acceptability of deleting ocular tests from protocol PALO-99-07 as submitted in Serial # 160.
January 31, 2003	IND 39,797	Telephone to Mr. Brian Strongin	Status of requested regarding acceptability of pediatric study PALO-99-07 protocol amendment # 2 (Serial # 160) to remove ocular function tests based on results of juvenile rat and dog tox reports also in Serial # 160.
February 4, 2003	IND 39,797	Amendment # 161	Appeal for reconsideration of proposed tradename ONICIT™.
February 27, 2003	IND 39,797	Amendment # 162	Request for feedback regarding proposed transfer of sponsor's IND obligations involving Helsinn (IND sponsor), MGI (clinical trial manager), and a CRO to conduct a clinical trial.
February 27, 2003	IND 39,797	Amendment # 163	Pediatric protocol amendment: new investigators for PALO-99-07.
March 12, 2003	IND 39,797	Telephone to/from Mr. Brian Strongin	DMETS request for identification of proposed market dose for IV Palo regarding CINVEX proprietary name review. Status of requested FDA review of PALO-99-07 protocol amendment # 2 (IND serial # 160, 20 Jan 03). Status of requested FDA feedback regarding transfer of sponsor's IND obligations, Helsinn-

			MGI-CRO (IND serial # 162, 27 Feb 03).
March 24, 2003	IND 39,797	Amendment # 164	Protocol amendment, new protocol, phase 1 protocol PALO-02-12.
March 27, 2003	IND 39,797	Fax from Dr. Justice	Letter from FDA re: Status Dr. Justice's decision regarding proposed proprietary name CINVEX™; Use of the proposed tradename, ALOXI™; Revision of strength on the immediate container and carton labeling.
April 1, 2003	IND 39,797	Fax from Mr. Brian Strongin	CINVEX™ and ALOXI™ FDA DME TS Reviews.
April 7, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's fax of April 1, 2003, regarding location of efficacy data for study PALO-00-01 (Study 2330) in Palonosetron NDA 21-372.
April 8, 2003	IND 39,797	Amendment # 165	Pediatric Protocol Amendment: New Investigators for PALO-99-07.
April 8, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's faxed requests of March 28, 2003 for rat and mouse carcinogenicity studies historical control data and (2) March 28, 2003, a separate fax, requesting clarification of the term "language on diary card" for Study PALO-99-03.
April 9, 2003	NDA 21-372	Amendment # 005	Chemistry, Manufacturing and Controls Contract Analytical Laboratory Change; Drug Product Site of Manufacture Name Change; Stability Update and Request for Extension of Expiration Date: request to extend the expiration date from 24 months to 36 months.
April 11, 2003	NDA 21-372	Telephone to/from Mr. Brian Strongin	FDA DMF deficiency letter faxed to Mr. Franco De Vecchi, US Agent for the DMF.
April 16, 2003	NDA 21-372	Fax to Mr. Strongin	Reply to FDA's faxed statistical requests of March 28, 2003, question # 1, (2) April 1, 2003, question # 2, (3) April 1, 2003, question # 3, and (4) April 7, 2003.
April 17, 2003	IND 39,797	Fax to Mr. Brian Strongin	New information regarding the proposed tradename, ALOXI.
April 21, 2003	NDA 21-372	Fax from Irma Rivera / FDA	Announce an inspection of Helsinn Advanced Synthesis in Biasca by an inspector of the US Food and Drug Administration.
April 24, 2003	NDA 21-372	Amendment # 006	Clinical, Statistical and Pharm/Tox: Replies to FDA faxed questions of March 28, April 1, and April 7, 2003.
April 30, 2003	IND 39,797	Amendment # 166	Chemistry, Manufacturing, and Controls.
May 1, 2003	NDA 21-372	Fax from Mr. Strongin	Statistical information request
May 9, 2003	IND 39,797	Amendment # 167	Pediatric Protocol Amendment: New Subinvestigators for PALO-99-07.

			Subinvestigators for PALO-99-07.
May 22, 2003	NDA 21-372	Teleconference	Statistical teleconference
May 30, 2003	NDA 21-372	Telephone from Mr. Strongin	Acceptability to FDA actions regarding treatment allocation data and proposed permutation testing for PALO-99-03, PALO-99-04, and PALO-99-05, as discussed during the FDA Statistical teleconference held 22 May 03.
June 3, 2003	NDA 21-372	Telephone to Mr. Strongin	Notification to FDA that Helsinn has acquired the name ALOXI and will proceed with the tradename ALOXI. PALO-99-07, Protocol Amendment # 2. Status of phase 3 efficacy treatment allocation information requested by FDA statistical reviewers during FDA statistical teleconference May 22, 2003.
June 4, 2003	IND 39,797	Amendment # 168	Protocol Amendment # 2. Pediatric Protocol PALO-99-07.
June 4, 2003	NDA 21-372	Letter to Mr. Justice	Helsinn acquisition of the tradename Aloxi™.
June 4, 2003	NDA 21-372	Fax from Mr. Strongin	CMC Information Request
June 5, 2003	IND 39,797	Amendment # 169	Investigator's Brochure.
June 6, 2003	NDA 21-372	Letter to Mr. Justice	Sponsor's reply to FDA Reviewing Chemist Dr. Kowblansky's CMC requests of June 5, 2003.
June 9, 2003	NDA 21-372	Amendment # 007	Statistical Information Requested by FDA during the teleconference held May 22, 2003.
June 10, 2003	IND 39,797	Amendment # 170	Protocol Amendment, New Protocol, Phase 1 Protocol PALO-03-05.
June 13, 2003	NDA 21-372	Fax to Mr. Strongin -	Sponsor's replies to FDA's pharmacology questions of June 11, 2003.
June 13, 2003	NDA 21-372	Amendment # 008	Chemistry, Manufacturing and Controls (CMC); sponsor's response to CMC questions in FDA's fax dated June 4, 2003.
June 16, 2003	NDA 21-372	Amendment # 009	Statistical information requested by FDA during the teleconference held May 22, 2003; results of permutation tests for PALO-99-03, PALO-99-04 and palo-99-05.
June 17/18, 2003	NDA 21-372	Telephone from Mr. Strongin	FDA request for a CMC teleconference on Thursday, June 19, 2003, 9:00 AM EDT to discuss the Sponsor's reply to FDA's CMC questions of June 4, 2003 (Sponsor's reply in NDA Amendment # 9).
June 18, 2003	NDA 21-372	Amendment # 010	Sponsor's reply to FDA's pharmacology questions of June 11, 2003.
June 20, 2003	NDA 21-372	Amendment # 011	Sponsor's reply to CMC requests in FDA teleconference held June 19, 2003.
June 25, 2003	NDA 21-372	Amendment # 012	Chemistry, Manufacturing and controls: Proposed revisions to immediate container (vial), carton and shipper labels.
June 26, 2003	IND 39,797	Amendment # 171	Proposed pediatric study request.

June 27, 2003	NDA 21-372	Fax to Mr. Strongin	Information request regarding vial label
June 30, 2003	IND 39,797	Amendment # 172	Pediatric Study PALO-99-07; Change in Safety Officer to Sean X. Wang, MD.
June 30, 2003	NDA 21-372	Telephone to/from Mr. Strongin	FDA urgent request for additional of storage conditions to the vials label. Revisions of vial labels. Revisions to vial labels – teleconference with Dr. Kowblansky, FDA Chemistry Reviewer.
July 1, 2003	NDA 21-372	Amendment # 013	Chemistry, Manufacturing and controls: Proposed additional revisions to immediate container (vial) label.
July 3, 2003	NDA 21-372	Fax from Mr. Strongin	Information request regarding QTc Prolongation in Pediatric Patients in PALO-99-07.
July 7, 2003	NDA 21-372	Letter from FDA	FDA minutes of teleconference held June 11, 2003, between representatives of Helsinn Healthcare SA and FDA to obtain clarifications regarding Study PALO-02-01.
July 9/10, 2003	IND 39,797	Telephone to/from Mr. Brian Strongin	Preliminary reply to FDA's request of July 3, 2003, re pediatric study PALO-99-07 ECG data. FDA receipt of PALO-99-07 ECG data in Sponsor's fax dated July 9, 2003.
July 9/10, 2003	NDA 21-372	Telephone/fax to/from FDA	Clarification of Table 3.8.4:8 regarding QTc values, and associated narrative in Volume 1.1 of the NDA. Schedule for FDA to provide a mark-up of labeling. Reply to Dr.Nair's ECG questions about Volume 1.1, page 220, Table 3.8.4:8 and narrative on that page of the NDA.
July 11, 2003	IND 39,797	Amendment # 173	Sponsor's reply to FDA request for ECG and related data for pediatric subjects enrolled in PALO-99-07.
July 14, 2003	NDA 21-372	Fax from FDA	Revision to FDA Market-Up Labeling for NDA 21-372 Faxed/E-mailed 7/11/03.
July 17/18, 2003	NDA 21-372	Telephone/Letter to/from FDA	Labeling revisions. Notification to FDA of impending submission of NDA Amendment # 14 and content. FDA schedule for issuance of an FDA decision letter for the NDA. Status of 2330 PK gender analysis. Dr.Nair request for information. Status of NDA 21-372 Amendment # 14. Status of PK data.
July 22, 2003	NDA 21-372	Telephone to/from FDA	Labeling revisions.
July 22, 2003	NDA 21-372	Amendment # 015	Proposed labeling revisions and FDA requested Study 2330 PK data.
July 24, 2003	NDA 21-372	Amendment # 016	Proposed labeling revisions.

July 24, 2003	NDA 21-372	Telephone to/from Mr. Strongin	Labeling revisions.
July 25, 2003	NDA 21-372	Letter from Dr. Beitz/FDA	Approval of NDA 21-372

12. **Statement of Eligibility of the Patent for Extension**

35 U.S.C. § 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if the following requirements (1)-(5) are satisfied:

(1) the term of the patent has not expired before an application for extension is submitted.

The term of U.S. Patent No. 5,202,333 expires on April 13, 2010. This application has been submitted before the expiration of the patent term. Accordingly, this requirement is satisfied.

(2) the term of the patent has never been extended.

The term of U.S. Patent No. 5,202,333 has never been extended. Accordingly, this requirement is satisfied.

(3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d).

This application is submitted by an agent of the owner of record, Roche Palo Alto LLC. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date that the product received permission for commercial marketing under the Federal Food, Drug, and Cosmetic Act and contains the information required under 35 U.S.C. § 156(d). Accordingly, this requirement is satisfied.

(4) the product has been subject to a regulatory review period before its commercial marketing or use.

As evidenced by the July 25, 2003, letter from FDA, see Attachment H, the product was subject to a regulatory review period under § 505 of the FDCA before its commercial marketing or use.

Accordingly, this requirement is satisfied.

(5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

The permission for the commercial marketing and use of palonosetron hydrochloride granted July 25, 2003, after regulatory review by FDA, is the first permitted commercial marketing or use of the product in the United States. Accordingly, this requirement is satisfied.

Because each of these requirements is satisfied, this patent is eligible for an extension.

#### **Statement as to Length of Extension Claimed**

The term of U.S. Patent 5,202,333 should be extended by 1827 days, or until April 13, 2015.

The length of extension was determined as follows:

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

(i) the period beginning on the date an exemption under subsection (i) of section 505 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 505.

An Investigational New Drug exemption (IND 39,797) became effective for the product on December 22, 1992. The New Drug Application for the product (NDA 21-372) was submitted on September 27, 2002. Thus, for the purpose of this calculation, period (i) for the product equals the number of days from December 22, 1992, to September 27, 2002, or 3566 days.

(ii) the period beginning on the date the application was initially submitted for the approved product under subsection (b) of section 505 and ending on the date such application was approved under such section.

The NDA for the product was submitted on September 27, 2002. The NDA was approved on July 25, 2003. Thus, for the purpose of this calculation, period (ii) equals the number of days from September 27, 2002 to July 25, 2003, or 301 days.

Under 35 U.S.C. § 156(c), the entire regulatory review period of 3867 days -- the sum of (i) and (ii) above, is reduced by the number of days in the regulatory review period which were on or before the date on which the patent issued. The regulatory review period for the product began on December 22, 1992. U.S. Patent No. 5,202,333 issued on April 13, 1993. The period from December 22, 1992 to April 13, 1993 is 112 days. Therefore, the regulatory review period is calculated as follows:  $3867 - 112 =$  3755 days.

35. U.S.C. § 156(c) also sets forth the following exceptions (1)-(3) which operate to shorten the length of the review period used to calculate patent term extension:

(1) the review period is reduced by any period during which the applicant did not act with due diligence.

Development was halted for business reasons during the time spanned by the filing of Amendments 051 to 053. See item 11 at page 14. Amendments 050 to 053 were filed, as required. Ownership of the IND was transferred in 1998, as shown in Amendments 054 and 055. At no time did applicant abandon or withdraw the IND or NDA or fail to file required reports, and therefore applicant has not made a deduction in the review period for lack of due diligence.

(2) the review period includes only one-half of the number of days in phase (i) which occurred after the date the patent issued.

Period (i) as calculated above is 3566 days. The number of days between issuance of the patent and initiation of the IND, as calculated above, is 112 days. Therefore, one-half the number of days determined to be in phase (i) after the patent issued is  $[(3566-112)/2]$  or 1727 days.

The maximum permissible extension is calculated by adding the 1727 days of period (i) to the 301 days of period (ii), for a total of 2028 days.

(3) if the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

The product was approved on July 25, 2003. US Patent No. 5,202,333 presently is set to expire on April 13, 2010. Thus, the patent term remaining after the date of product approval is the period between July 25, 2003 and April 13, 2010, or 2454 days. When 2454 days is added to the regulatory review period as revised above, 2028 days, the total is 4482 days or 12.5 years, which does not exceed 14 years. Therefore, this limitation does not apply.

35 U.S.C. § 156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent 5,202,333 is April 13, 2010. Accordingly, the maximum extension allowed by this provision would extend the term to April 13, 2015. Extension of the patent by the number of days calculated above would extend the patent beyond April 13, 2015. Accordingly, pursuant to 35 U.S.C. § 156(g)(6), U.S. Patent 5,202,333 cannot be extended beyond April 13, 2015.

**Thus, U.S. Patent No. 5,202,333 is entitled to an extension until April 13, 2015, or 1827 days.**

**13. Duty of Disclosure**

Applicant acknowledges a duty to disclose to the Director of the US Patent & Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought herein.

**14. Fees**

A check for \$1120 (37 CFR 1.20(j)(1)) is enclosed. The Director is hereby authorized to charge any underpayment or credit any overpayment to Deposit Account No. 08-1641, referencing 13265-1163.

**15. Name and address for correspondence**

Inquiries and correspondence relating to this Application for interim extension of patent term should be directed to:

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16. **Multiple copies**

This Application for extension of patent term is being submitted in an original and two copies. The undersigned hereby certifies that the copies of this Application (together with the appended Attachments A through H) filed herewith are true and correct copies.

Respectfully submitted,



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