DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022445

NDA APPROVAL

Heron Therapeutics, Inc.
Attention:
Michael A. Adam, Ph.D.
123 Saginaw Drive
Redwood City, CA 94063

Dear Dr. Adam:

Please refer to your New Drug Application (NDA) dated May 16, 2009, received May 18, 2009 , and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sustol (granisetron) extended-release injection, for subcutaneous use, 10 mg/0.4mL.

We also refer to our approval letter dated August 9, 2016 which contained the following error: Post Marketing Commitments 3094-5 and 3094-6 were listed as Post Marketing Commitments not subject to the reporting requirement under section 506B when they should have been listed as postmarketing commitments subject to the reporting requirements under section 506B.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain August 9, 2016, the date of the original approval letter.

We acknowledge receipt of your amendment dated July 16, 2015, which constituted a complete response to our March 27, 2013, action letter.

NDA 022445 provides for the use of Sustol (granisetron) extended-release injection, for subcutaneous use, [redacted] (b) (4) we have designated as follows:

- NDA 022445/Original 1 - SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

[redacted] (b) (4)

The subject of this action letter is NDA 022445/Original 1. [redacted] (b) (4)

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Instructions for Use, and text for the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

We acknowledge your August 9, 2016, submission containing final printed carton and container labels.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and/or carton and immediate container labels submitted on August 9, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 022445." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Brian Strongin, R.Ph., MBA
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building #22,
Room: 5116
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS (e.g., UPS, DHL), please send to:

Brian Strongin, R.Ph., MBA
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building #22,
Room: #5116
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

ADVISORY COMMITTEE

Your application was not referred to an FDA advisory committee because Sustol (granisetron) extended-release injection, for subcutaneous use is not the first drug in its class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring submission of your pediatric studies for ages birth to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. These required studies are listed below.

3094 - 1 A pharmacokinetic/dose ranging study to determine the pediatric doses of Sustol (granisetron) extended-release injection, for subcutaneous use, and a controlled clinical trial with an active comparator to evaluate the efficacy, safety, and tolerability of Sustol (granisetron) extended-release injection, for subcutaneous use, for the prevention of acute and delayed phase nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens in pediatric patients ages 12-17 years old.

Final Protocol Submission:	06/2017
Study Completion:	11/2022
Final Report Submission:	03/2023

3094 – 2 A pharmacokinetic/dose ranging study to determine the pediatric doses of Sustol (granisetron) extended-release injection, for subcutaneous use, and a controlled clinical trial with an active comparator to evaluate the efficacy, safety, and tolerability for the prevention of acute and delayed phase nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens in pediatric patients ages 0 to less than 12 years old.

Final Protocol Submission:	06/2019
Study Completion:	11/2024
Final Report Submission:	03/2025

3094 - 3 A 1-month, GLP juvenile animal toxicology study of Sustol (granisetron) extended-release injection, for subcutaneous use, conducted in a single species. This study must be completed and submitted for review before initiating pediatric studies in patients ages 0 to less than 12 years.

Final Protocol Submission:	11/2017
Study Completion:	11/2018
Final Report Submission:	03/2019

Submit the protocol(s) to your IND 068213, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of injection site reactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of injection site reactions with the use of Sustol (granisetron) extended-release injection, for subcutaneous use.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3094 – 4 A repeat dose, randomized, active-controlled trial to assess the safety of Sustol (granisetron) extended-release injection, for subcutaneous use, when administered to patients receiving chemotherapy, for 6 cycles.

The timetable you submitted on 6/9/2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2017
Trial Completion:	03/2021
Final Report Submission:	09/2021

Submit the protocol(s) to your IND 068213, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "Required Postmarketing Protocol Under 505(o)," "Required Postmarketing Final Report Under 505(o)," "Required Postmarketing Correspondence Under 505(o)."

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3094 - 5 A 2-year subcutaneous carcinogenicity study in rats with the (b) (4) vehicle used in the formulation of Sustol (granisetron) extended-release injection, for subcutaneous use.

The timetable you submitted on 6/9/2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 11/2017
Study Completion: 06/2020
Final Report Submission: 01/2021

3094 – 6 A Syrian Hamster Embryo (SHE) cell transformation assay with the (b) (4) vehicle used in the formulation of Sustol (granisetron) extended-release injection, for subcutaneous use.

The timetable you submitted on 6/9/2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2017
Study Completion: 04/2018
Final Report Submission: 10/2018

3094-7 An addition to the stability protocol to test the break force, glide force, and peak force of injection of Sustol (granisetron) extended-release injection, for subcutaneous use.

The timetable you submitted on 02/18/2016, states that you will conduct this study according to the following schedule:

Final Report Submission: September 09/2018

Submit clinical protocols to your IND 068213 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

OPDP Regulatory Project Manager
Food and Drug Administration

Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that, for a period of two years, you submit, as 15 day alert reports, all cases of injection site reactions requiring medical attention by a healthcare provider (emergency room, urgent care center, inpatient hospitalization, or unscheduled clinic visit) and inpatient hospitalizations due to gastrointestinal conditions, including constipation, gastrointestinal obstruction, ileus, pancreatitis, and gastrointestinal perforation. Provide detailed analyses of these clinical study and post-marketing reports as adverse events of special interest in your Periodic Benefit- Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of Sustol (granisetron) extended-release injection, for subcutaneous use, as well as relative to the prior PBRER. Medical literature reviews for case reports/case series of these reactions should also be provided in the PBRER.

If you have any questions, call Brian Strongin, R.Ph., MBA, Chief Regulatory Project Management Staff, at (301) 796-1008

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director

Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

DONNA J GRIEBEL
08/09/2016