DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020239/S-023

SUPPLEMENT APPROVAL

Hoffmann-La Roche Inc.
Attention: Anthony J. Corrado
Director, Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Mr. Corrado:

Please refer to your Supplemental New Drug Application (sNDA) dated March 30, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kytril (granisetron hydrochloride) Intravenous Injection.

We acknowledge receipt of your amendments dated June 9, 2010; June 24, 2010; October 13, 2010; November 11, 2010; April 4, 2011; April 19, 2011; and April 28, 2011.

This "Prior Approval" supplemental new drug application provides for:

- updates to the package insert label with information from pediatric study report ML16633, "Intravenous Granisetron (Kytril) in the Prevention of Post-operative Nausea and Vomiting (PONV) in Pediatric Subjects Undergoing Tonsillectomy or Adenotonsillectomy."
- conversion of the package insert label to Physician Labeling Rule (PLR) format.

We have completed our review of this supplemental application, as amended. The package insert label was updated to include information from pediatric study ML16633. This study did not support inclusion of dosage and administration instructions in the package insert label for prevention of PONV in pediatric patients ages 2 years to 16 years. The supplement 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), with the

addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels 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 "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 020239/S-023**." Approval of this submission by FDA is not required before the labeling is used.

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 indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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.

Since Kytril (granisetron hydrochloride) Injection was approved on December 29, 1993, we have become aware of positive results from a randomized, single-dose, double-blind, placebo-controlled, cross-over, single-center clinical trial which studied the QT interval prolongation with a selective serotonin 5-HT3 receptor antagonist. FDA reviewed the results of this trial and believes that the class of selective serotonin 5-HT3 receptor antagonists, of which Kytril (granisetron hydrochloride) Injection is a member, may cause QT interval prolongation. Significant QT interval prolongation may cause life threatening cardiac arrhythmias and/or sudden death.

Additionally, QT prolongation was reported in your pediatric PONV study ML16633. As this was not a dedicated QT study, results were confounded by lack of placebo control, concomitant medications, and the postoperative state. Therefore, an adequate study must be conducted to further characterize the QT effects of granisetron.

We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 the serious risk of prolongation of the QT interval.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA is not yet 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 serious risk of prolongation of the QT interval.

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

1732-1 A randomized, double-blind, placebo-controlled and active-controlled, four-period crossover trial, of two doses of granisetron, a positive control (moxifloxicin 400 mg), and placebo to assess the risk of QT prolongation. The supratherapeutic dose of granisetron in this study should cover high exposure scenarios expected with oral and I.V. formulations in the adult and pediatric patient populations.

The timetable you submitted on April 19, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2012
Trial Completion:	April 2015
Final Report Submission:	April 2016

Submit the protocol to your IND 031707, 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 commitment:

1732-2 Conduct an adequate and well-controlled trial to evaluate the efficacy of intravenous granisetron for the prevention of postoperative nausea and vomiting in pediatric patients 0 to 16 years of age. The trial must include an active-control arm. The trial should include assessment of granisetron pharmacokinetics and safety.

The timetable you submitted on April 19, 2011, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	April 2012
Study/Trial Completion:	April 2015
Final Report Submission:	April 2016

Submit clinical protocols to your IND 031707 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study 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 the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), 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).

If you have any questions, call Jagjit Grewal, Regulatory Project Manager, at (301) 796-0846.

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: Package Insert Label
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
04/29/2011