SmithKline Beecham Pharmaceuticals
Attention: Olivia Pinkett, PhD
Director, NA Regulatory Affairs
1250 S. Collegeville Road,P.O. Box 5089
Collegeville, PA 19426-0989

Dear Dr. Pinkett:

Please refer to your supplemental new drug application dated July 27, 1998, received July 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Kytril (granisetron HCL) Tablets.

We acknowledge receipt of your submissions dated August 10, 20, 25, September 1 and 25, October 15 and 22, 1998, January 27, February 26, May 19 and 26, 1999.

This supplemental new drug application provides for the use of Kytril (granisetron HCL) Tablets for prevention of nausea and vomiting associated with radiation, including total body irradiation (TBI) and fractionated abdominal radiation.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted July 27, 1998, immediate container and carton labels submitted January 27, 1999) with the revisions listed below. Accordingly, the supplemental application is approved effective on the date of this letter.

The package insert should be revised to contain the following CLINICAL TRIALS SECTION:

Radiation-Induced Nausea and Vomiting:

Total Body Irradiation: In a double-blind randomized study, 18 patients receiving *Kytril* Tablets, 2.0 mg daily, experienced significantly greater antiemetic protection compared to patients in a historical negative control group who received conventional (non-5-HT_3 antagonist) antiemetics. Total body irradiation consisted of 11 fractions of 120 cGy administered over 4 days, with three fractions on each of the first 3 days, and two fractions on the fourth day. *Kytril* Tablets were given one hour before the first irradiation fraction of each day.

Twenty-two percent (22%) of patients treated with *Kytril* Tablets did not experience vomiting or receive rescue antiemetics over the entire 4-day dosing period, compared to 0% of patients in the historical negative control group ($P<0.01$).

In addition, patients who received *Kytril* Tablets also experienced significantly fewer emetic episodes during the first day of radiation and over the 4-day treatment period, compared to patients in the historical negative control group. The median time to the first emetic episode was 36 hours for patients who received *Kytril* Tablets.

***Fractionated Abdominal Radiation*:** The efficacy of *Kytril*, 2 mg daily, was evaluated in a double-blind, placebo-controlled randomized trial of 260 patients. *Kytril* Tablets were given 1 hour before radiation, composed of up to 20 daily

fractions of 180 to 300 cGy each. The exceptions were patients with seminoma or those receiving whole abdomen irradiation who initially received 150 cGy per fraction. Radiation was administered to the upper abdomen with a field size of at least 100 cm^2.

The proportion of patients without emesis and those without nausea for Kytril tablets, compared to placebo were statistically significant ($p<0.0001$) at 24 hours after radiation, irrespective of the radiation dose. Kytril was superior to placebo in patients receiving up to 10 daily fractions of radiation, but was not superior to placebo in patients receiving 20 fractions.

Patients treated with *Kytril* Tablets (n=134) had a significantly longer time to the first episode of vomiting (35 vs. 9 days, $P<0.001$) relative to those patients who received placebo (n=126), and a significantly longer time to the first episode of nausea (11 vs. 1 day, ($P<0.001$). *Kytril* provided significantly greater protection from nausea and vomiting than placebo.

The non-commercial package insert should be identical to the commercial, revised to delete any reference to the 1 mg tablet and the associated dosage regimen, with the exception that the HOW SUPPLIED section should accurately reflect the available product(s).

These revisions are terms of the approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-305/S-004." Approval of this submission by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2001. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Kati Johnson, Supervisor, Project Management Staff, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research