DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-107/S-012

SmithKline Beecham Corporation d/b/a/ GlaxoSmithKline
Attention: Robert J. Bohinski
Associate Director, Respiratory, US Regulatory Affairs
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

Dear Mr. Bohinski:

Please refer to your supplemental new drug application dated September 12, 2005, received September 13, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex® (alosetron hydrochloride) Tablets.

We also refer to your submission dated June 23, 2005, received June 24, 2005, containing the full study report for postmaketing commitment #5 titled "An open-label, parallel-group, pharmacokinetic and tolerability study of a single 1mg dose of alosetron in hepatically-impaired subjects and in healthy control subjects."

We also refer to your electronic mail dated March 6, 2006, in which you agreed to the following revisions (double underlines indicate additions and strikeouts indicate deletions):

> ***Reduced Hepatic Function:*** A single 1mg oral dose of alosetron was administered to 1 female and 5 male patients with moderate hepatic impairment (ChildPugh score of 7 to 9) and to 1 female and 2 male patients with severe hepatic impairment (ChildPugh score of >9). In comparison with historical data from healthy subjects, patients with severe hepatic impairment displayed higher systemic exposure to alosetron. The female with severe hepatic impairment displayed approximately 14 fold higher exposure ~~than healthy females,~~ while the female with moderate hepatic impairment displayed approximately 1.6-fold higher exposure, than healthy females. ~~and the 2 males with severe hepatic impairment displayed approximately 2.4fold higher exposure than healthy males. C_{max} and T_{max} did not differ as much between patients with severe hepatic impairment and healthy subjects. No clear effect of moderate hepatic impairment was observed, although halflife was prolonged in patients with either moderate or severe hepatic impairment compared with halflife in healthy subjects.~~ Due to the small number of subjects and high intersubject variability in the pharmacokinetic findings, no definitive quantitative conclusions can be made. However, due to the greater exposure to alosetron in the female with severe hepatic impairment, alosetron should not be used in females with severe hepatic impairment (see CONTRAINDICATIONS, PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment).

Hepatic Insufficiency: Due to the extensive hepatic metabolism of alosetron, increased exposure to alosetron and/or its metabolites is likely to occur in patients with hepatic insufficiency. Alosetron should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment (see CLINICAL PHARMACOLOGY: Population Subgroups: *Reduced Hepatic Function*).

Patients With Hepatic Impairment: LOTRONEX is extensively metabolized by the liver and increased exposure to LOTRONEX is likely to occur in patients with ~~moderate to severe~~ hepatic impairment. Increased drug exposure may increase the risk of serious adverse events. LOTRONEX should be used with caution in patients with mild or moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment (see CLINICAL PHARMACOLOGY: Population Subgroups: *Reduced Hepatic Function*, CONTRAINDICATIONS, and PRECAUTIONS: Hepatic Insufficiency).

This supplemental new drug application provides for the addition of information to the package insert regarding the hepatically impaired population.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-107/S-012**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Susan Daugherty, Regulatory Project Manager, at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Joyce Korvick
3/10/2006 12:03:31 PM
for Dr Brian Harvey