

NDA 21-107

Glaxo Wellcome Inc.  
Attention: Mark Baumgartner, RPh  
Product Director, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Mr. Baumgartner:

Please refer to your new drug application (NDA) dated June 29, 1999, received June 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) Tablets.

We acknowledge receipt of your submissions dated August 10, 20, 23, 25, 27, and 30; September 1, 2, 3, 10, 13, 14, 15, 17, 20, 21, 22, and 24; October 15, 25, 27, and 29; November 2, 12, 15, 19, and 30; December 1, 6, 7, and 22, 1999; and January 13, 17, and 21; February 7, and 8, 2000.

This new drug application provides for the use of Lotronex (alosetron hydrochloride) Tablets, 1 mg, for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. The safety and effectiveness of Lotronex in men have not been established.

We have completed the review of this 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 agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted February 8, 2000, immediate container and carton labels submitted December 6, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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 NDA 21-107." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated December 22, 1999 and January 24, 2000. These commitments, along with any completion dates

agreed upon, are listed below.

Conduct the following studies:

1. A large, long-term (1 year) population risk trial to assess the incidence of colitis in patients receiving alosetron.
2. A study to assess efficacy and safety in men with Irritable Bowel Syndrome.
3. In vitro assessment of alosetron or metabolites on cultured endothelial cell integrity. One possible model could assess whether the drug or metabolites could affect extracellular matrix synthesis and/or could induce apoptosis of endothelial cells of restricted lineage.
4. Additional studies to clarify the metabolism and disposition of alosetron in vivo. Specific issues that should be addressed include the formation of n-desmethyl-alosetron and its metabolites, especially in Asians, and identification of the unidentified circulating metabolites from the mass balance study.
5. A pharmacokinetic study in subjects with hepatic impairment. In addition to alosetron kinetics, metabolite kinetic data should also be examined.
6. In vitro pharmacology, drug metabolism, and drug interaction studies. These should include 5HT<sub>3</sub> receptor affinities for any circulating or major metabolites (including conjugates), identification of P450 isozymes responsible for the formation of specific metabolites, plus the effect of alosetron and its metabolites on N-acetyltransferase 1 (NAT1), monoamine oxidases, and P450 isozymes, as appropriate.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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)(21 CFR 314.55 (or 601.27)). FDA is deferring submission of the pediatric assessments of

safety and effectiveness that may be required under these regulations at this time since you have already indicated your intent, with your November 5 and December 20, 1999 Proposed Pediatric Study Requests, to pursue additional marketing exclusivity under the term of section 505A of FDAMA. These submissions are currently under review.

Submission of pediatric studies before you receive a Written Request may not fulfill the requirements for additional exclusivity. Please note that satisfaction of the requirements of 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

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

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, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

Victor F.C. Raczkowski, M.D., M.Sc.  
Deputy Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research