DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-515

GlaxoSmithKline
Attention: Mary E. Martinson
Director, Regulatory Affairs, Psychiatry
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Martinson:

Please refer to your new drug application (NDA) dated August 26, 2002, received August 26, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin XL (bupropion hydrochloride extended-release) Tablets.

We acknowledge receipt of your submissions dated July 3, 2003, August 21, 2003, and August 28, 2003. The July 3, 2003 submission constituted a complete response to our June 24, 2003 action letter.

This new drug application provides for the use of Wellbutrin XL (bupropion hydrochloride extended-release) tablets as a new extended-release formulation of bupropion.

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 agreed-upon labeling text.

Labeling

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

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 NDA 21-515**." Approval of this submission by FDA is not required before the labeling is used.

Drug Product Expiry

The expiration date presently approved for Wellbutrin XL 150 mg and 300 mg Tablets in the 7 and 30 count bottle is 12 months.

Dissolution Specifications

Following is the approved *in vitro* dissolution specifications for both strengths of Wellbutrin XL 150 mg and 300 mg tablets:

Apparatus:	USP Apparatus 1 (Basket) at 75 RPM	
Medium:	900mL of 0.1N hydrochloric acid at 37± 0.5°C	
Specifications:	2 hours:	(b)(4)
	4 hours:	(b)(4)
	8 hours:	(b)(4)
	16 hours:	(b)(4)
Sample size:	12 tablets for each time point in the dissolution profile	

Risk Management Plan and Post-Marketing Commitment

We have reviewed your proposed risk management plan included in the July 3, 2003 submission and overall, find your proposal to be acceptable. However, as discussed with you, we consider the Healthcare Practitioner letters and Educational Communication Plan to be essential components of this risk management plan and remind you of your postmarketing commitment dated August 28, 2003. This commitment is listed below.

> Educational Communication Plan: We note your agreement to provide all components of your Educational Communication Plan for Wellbutrin XL (bupropion hydrochloride extended-release tablets) on or before December 15, 2003.
>
> Please submit these educational materials as a package to the NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected completion dates and any changes in plans since the last annual report. All submissions, including supplements, relating to this postmarketing commitment must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

Finally, we recommend the following labeling revisions for your companion NDA for Wellbutrin SR Tablets (NDA# 20-358) to minimize potential errors with the use of Wellbutrin XL Tablets since there is a potential for confusion between the two products:

- Include "twice-a-day" text on container labels and carton labeling of the marketed product Wellbutrin SR Tablets (NDA 20-358). (Due to the 150 mg daily initial dosing for Wellbutrin SR Tablets, we recommend that this labeling statement be accompanied by a reference to full dosing information [e.g., "See package insert for full dosage information."])

Patient Education

We also have the following recommendations regarding patient education and related materials:

- All patient information materials (e.g., tear-off sheets, brochures, website, etc.) should contain language that is consistent with the patient package insert (PPI).
- Healthcare providers should be encouraged to provide appropriate education regarding Wellbutrin XL Tablets to their patients, and to reinforce this information by providing the patient with a PPI. Our rationale for this recommendation is below.

  With a few exceptions, PPIs are not required by law to be distributed at time of dispensing. PPIs are discretionary and usually do not accompany prescription medicines at the time of

dispensing for various reasons. Wellbutrin XL will be supplied in bottles of 30 as 150 mg or 300 mg tablets. Even if the PPI is packaged with these bottles, the following factors may diminish the percentage of patients receiving a PPI. The dose of Wellbutrin XL ranges from 150 mg to 450 mg per day. Pharmacies may repackage medications from these packaged amounts when the prescribed amount differs from the packaged amount, or when they have a low supply of the medication on hand and can only dispense a partial prescription.

Methods Validation

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Neuropharmacological Drug products and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

MedWatch-to-Manufacturer Program

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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 Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
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/

Russell Katz
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