



NDA 18-644/S-022/S-023
NDA 20-358/S-018/S-023

Glaxo SmithKline
Attention: James Murray
Director Regulatory Affairs
Five Moore Drive
Research Triangle Park, NC 27709

Dear Mr. Murray:

Please refer to your supplemental new drug applications dated May 26, 2000 (18-644/S-022 and 20-358/S-018), and February 8, 2001 (18-644/S-023 and 20-358/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin (bupropion hydrochloride) 75 mg and 100 mg Immediate-Release Tablets (NDA 18-644) and Wellbutrin SR (bupropion hydrochloride) Sustained-Release 100 mg and 150 mg Tablets (NDA 20-358).

We additionally refer to Agency approvable letters dated July 31, 2001 for applications 18-644/S-022 and 20-358/S-018, and August 27, 2001 for applications 18-644/S-023 and 20-358/S-023.

We acknowledge receipt of your complete responses dated October 12, 2001 (18-644/S-022 and 20-358/S-018), and October 10, 2001 (18-644/S-023 and 20-358/S-023), to the above action letters.

We additionally refer to an electronic communication from you to Mr. Paul David, of this Agency, dated June 10, 2002, agreeing to implement the revisions to labeling, as stated below, which were submitted under 18-644/S-022 and 20-358/S-018.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as agreed upon and stated below. Accordingly, these supplemental applications are approved effective on the date of this letter.

These supplemental new drug applications provide for the following revisions to product labeling:

18-644/SLR-022

20-358/SLR-018

These supplements provide for revisions to the labeling to incorporate the results of pharmacokinetic and tolerability studies for the use of bupropion in patients with liver cirrhosis.

[All of your proposed changes are acceptable except for those changes noted below which were agreed upon in an electronic communication dated June 10, 2002. Double underline font denotes additions to the labeling and strike through font denotes deletions to the labeling.]

WELLBUTRIN ONLY LABELING CLINICAL PHARMACOLOGY

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of the individual enantiomers have not been studied. In humans, following oral administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved within 2 hours, followed by a biphasic decline. The terminal phase has a mean half-life of 14 hours, with a range of 8 to 24 hours. The distribution phase has a mean half-life of 3 to 4 hours. The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 (\pm 9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma levels are maintained in chronic use.

WELLBUTRIN & WELLBUTRIN SR LABELING

The second paragraph in the Population Subgroups-Hepatic subsection, starting with the 4th sentence, should be changed as follows:

The mean AUC increased by ~~28~~ about 1 1/2 fold for hydroxybupropion and ~~50~~ about 2 1/2 fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and ~~24~~ 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 4 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

18-644/SLR-023

20-358/SLR-023

These supplements provide for labeling revisions to the **ADVERSE REACTIONS-Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: Hemic and Lymphatic** section of labeling as requested in an Agency letters dated November 28, 2000, and August 27, 2001.

Additionally, we agree with your response to not submit, in an expedited fashion, new reports of alterations in PT and/or INR with or without hemorrhagic or thrombotic complications in patients taking concomitant bupropion and warfarin. Your proposal to include an annual review and analysis of all such reports in the annual Periodic Report for bupropion is acceptable provided that you agree to conduct this review and analysis for all bupropion products, i.e., Wellbutrin immediate release, Wellbutrin sustained-release, and Zyban.

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplements 18-644/S-022

and 20-358/S-0018" Approval of these submissions by FDA is not required before the labeling is used.

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, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

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

**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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