

021515/000 - Original - Approval, Pkg

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-515

Trade Name: Wellbutrin XL Tablet

Generic Name: Bupropion HCl

Sponsor: GlaxoSmithKline

Approval Date: August 28, 2003

Indications: Provides for the use of Wellbutrin XL tablets as a new extended-release formulation of bupropion.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-515

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter 1	X
Approvable Letter 2	
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-515

APPROVAL LETTER



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
8/28/03 03:22:12 PM

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-515

APPROVABLE LETTER 1



NDA 21-515

GlaxoSmithKline
Attention: Mary E. Martinson,
Director, Psychiatry Regulatory Affairs, 5.5206
PO 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) Extended-Release Tablets, 150 mg and 300 mg. This NDA provides for a new extended-release formulation of bupropion.

We also acknowledge receipt of your amendments dated:

December 18, 2002 (2)	January 15, 2003	January 24, 2003
February 11, 2003	April 15, 2003	April 17, 2003(2)
May 30, 2003	June 6, 2003	

We have completed the review of this application as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments and requests.

Proposed Trademark Wellbutrin XL

We note the submission of your proposed trademark, Wellbutrin XL, for this drug product. It has been reviewed by the Office of Drug Safety / Division of Medical Errors and Technical Support and by the Division of Drug Marketing, Advertising, and Communications, which have no objections to the proposed trademark. DMETS does, however, have concerns regarding potential medication errors occurring among Wellbutrin XL, Wellbutrin SR, Wellbutrin, and Zyban.

The addition of a modifier (XL) will not guarantee differentiation within the product line, especially since there will be two extended release formulations on the market when this NDA is approved (XL and SR). Since the XL and SR products are not bioequivalent, they cannot be interchanged. We are aware that there are nine other drug products currently using "XL" as a modifier' however, none of these has another extended-release formulation that could be confused with the XL formulation.

We are therefore concerned about the potential for confusion between Wellbutrin and Wellbutrin XL, based on medication error reports which have shown that there can be confusion between Wellbutrin and Wellbutrin SR, and about presumed interchangeability between Wellbutrin SR, Wellbutrin XL, and Zyban:

- A healthcare professional may be unaware that a new formulation of Wellbutrin is available and may therefore assume that a prescription for Wellbutrin XL is actually a prescription for Wellbutrin SR.
- Wellbutrin SR, Wellbutrin XL, and Zyban share a common strength (150 mg). Since Wellbutrin SR and Zyban are interchangeable, we are concerned that healthcare professionals may also assume that Wellbutrin XL can be interchanged with Wellbutrin SR or Zyban. If Wellbutrin XL is erroneously given twice daily, this could result in an increased risk of seizure to the patient.

Because of these concerns, DMETS recommends the creation and implementation of a risk management plan to educate healthcare professionals and patients on the appropriate use of Wellbutrin XL with respect to other marketed dosage forms of bupropion hydrochloride.

- Healthcare providers will need to be informed that a **new once daily** extended release formulation of bupropion will be available in the US marketplace.
- Healthcare providers will also need to be informed that there will be a 150 mg strength for Wellbutrin SR, Zyban, and Wellbutrin XL.
- Healthcare providers need to be educated regarding how the new extended release formulation should be administered to both new and established patients, and under what circumstances the extended release products can be interchanged.
- If healthcare providers switch a patient from Wellbutrin or Wellbutrin SR to Wellbutrin XL, the patient needs to fully understand the dosing schedule and the importance of not taking Wellbutrin XL more than once daily.

This plan should be implemented both before and after product launch. In addition, once this NDA is approved, you should submit any medication error reports associated with Wellbutrin XL to the Agency within 15 days of their receipt by your firm, whether the error is actual or potential.

Finally, it is CDER policy that proposed proprietary names and their associated labels must be evaluated approximately 90 days prior to the anticipated approval of the NDA. Since the Agency is not yet prepared to approve your application, full re-evaluation of your trademark will be necessary prior to final approval of the NDA. To this end, please assure that a complete set of mock-up container labels and labeling are provided, featuring the proposed trademark, in your complete response to this letter. (We also have comments and requests regarding the container labels: please see the heading **Labeling**, below.)

Chemistry, Manufacturing and Controls (CMC)

We have completed our review of your submission and have the following comments and requests for information:

1. Please provide a description of the bulk packaging process for the drug product.
2. In your sampling plan for the drug product, you indicate that representative samples of the drug product will be taken at the end of the manufacturing process to serve as a source of samples for testing. Please be advised that samples should be taken throughout the manufacturing process and not just at the end. Please provide an updated sampling plan which adequately tests samples of product from the beginning, middle, and end of the process.

3. The relative response factors associated with each impurity / degradant should be incorporated into the formulas used for calculating the impurity / degradant levels. The impurity / degradant levels should be recalculated using the relative response factors. In addition, the impurity / degradant limits should be recalculated for the drug product.
4. Provide a complete and detailed description of the secondary packaging systems for the _____ bottles _____. Your response should include specifications and in-process controls.
5. Please provide updated drug product stability information.

We have also incorporated the revised storage statement (previously agreed upon between yourselves and our chemistry review team) into the overall revised labeling (package insert) appended to this letter. Please address this change in all labeling elements, including container and carton labeling as well as the package insert, when submitting your complete response.

CMC: Methods Validation

We have not completed validation of the regulatory methods for this application. We will expect your continued cooperation to resolve any problems that may be identified.

CMC: Categorical Exclusion

We have completed our review of the Environmental Assessment information provided by your firm, and we agree with your request for a Categorical Exclusion from the requirement to perform a full Environmental Assessment for this application.

Clinical Pharmacology and Biopharmaceutics

1. Please adopt the following dissolution method and specifications for both strengths of Wellbutrin XL tablets. Note change in specifications at 4 and 8 hours:

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

2. Bupropion is hydroxylated by CYP2B6. Recently, *in vitro* studies have identified more substrates and inhibitors of CYP2B6, and the results of recent *in vitro* studies suggest that several SSRIs and antiretroviral drugs may inhibit the hydroxylation of bupropion by CYP2B6. It would be useful to characterize the requirement for dosing modifications, if necessary, when such drugs are given concomitantly with bupropion. Therefore we recommend that you conduct a thorough search of the literature, as well as searching adverse event reports for bupropion, to evaluate the potential for pharmacokinetic and/or pharmacodynamic (adverse event) drug interactions with bupropion and inhibitors/substrates such as paroxetine, sertraline, fluvoxamine, norfluoxetine, efavirenz, ritonavir, and

nelfinavir. Based on these literature results, an *in vivo* drug interaction study may be necessary.

In addition, we have made specific changes in the revised labeling appended to this letter. Please address these changes in your complete response.

Clinical / Clinical Safety

We have completed our review of the clinical safety information and proposed package insert as provided in your NDA. Our comments are incorporated into the revised labeling appended to this letter, as bracketed comments, text insertions [underlined], or deletions [strikethrough]. Please address these changes specifically in your complete response.

Request for Safety Update

In your complete response to this letter, please include a safety update as described in 21 CFR 314.50(d)(5)(vi)(b).

1. The safety update should include data from all non-clinical and clinical studies of the drug under consideration, regardless of indication, dosage form, or dose level.
2. Please describe in detail any significant changes or findings in the safety profile.
3. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, please incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the preceding bullet point.
4. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
5. Please present a retabulation of the reasons for premature study discontinuation by incorporating the dropouts from the newly completed studies. Describe any new trends or patterns identified.
6. Please provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, please provide narrative summaries for serious adverse events.
7. Please describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
8. Prior to an approval action, we require an updated report on the world's archival literature pertaining to the safety of Wellbutrin XL. Please provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries. This report should include only literature not covered in your previous submissions. We will need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Wellbutrin XL. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be

described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

Labeling (Package Insert and Container Labeling)

1. In addition to responding to the points listed above, it will be necessary for you to submit draft labeling revised as shown in the attachment to this letter. We believe the attached draft labeling presents a fair summary of the information available on the benefits and risks of Wellbutrin XL (bupropion) Extended Release Tablets in the treatment of major depressive disorder.

Please use the proposed text verbatim. You will see that we have proposed a number of changes to the draft labeling as updated in your January 24, 2003 submission, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff are willing to discuss these proposed changes in detail and to meet with you to discuss any disagreements you may have with any part of the proposed labeling format or content.

2. In addition, we have the following comments with respect to the container labeling for the new drug product:
 - A. Container Labeling (150 and 300 mg tablets, packages of 7 and of 30 tablets)
 1. The phrase "extended-release tablets" should be included within the brackets of the established name so that it reads: (bupropion hydrochloride extended-release tablets)
 2. The phrase "extended-release tablets" should appear in the same font as "bupropion HCl" and should be at least ½ the size of the proprietary name.
 3. The logo around the "XL" is distracting and should be deleted, or moved to a less prominent location. The strengths, "150 mg" and "300 mg", on the lids of the cartons that contain 12 bottles of 7 tablets should be made more prominent by, for example, increasing the font size.
 - B. Carton Labeling (carton containing 12 bottles of 7 tablets)
 1. Please see comments A.1. through A. 3. above.
 - C. Patient Sample Kit (1 bottle of 150 mg strength (7 tablets) and one bottle of 300 mg strength (7 tablets))
 1. The 150 mg tablets bottle (7 tablets) and the 300 mg tablets bottle (7 tablets) should not be packaged together. A dose of 300 mg per day is not initiated until Day 4 of dosing; a patient may easily confuse the two bottles and mistakenly take the wrong dose. For example, a patient may accidentally ingest a 300 mg tablet on Day 1 of dosing.
 2. Also, the tablets are similar in appearance (creamy-white to pale yellow), increasing the potential risk of taking the wrong strength at the wrong time when they are packaged together. This would increase the risk of seizures as well as other side effects such as agitation, insomnia, and psychosis.
 3. The [REDACTED] should be removed from the front panel, since it distracts attention

from the proprietary and established names of the drug as well as from the dosage strength(s).

4. The statements "Sample – Not for Sale" and "Patient Sample Kit" should be moved to the bottom of the front panel so that they do not distract from the proprietary and established names of the drug as well as the dosage strength(s).
- D. Shipping Carton (Contains 4 Sample Kits)
1. See comments C.1. through C.4., above.

Promotional Materials

In your complete response to this letter, please also submit three copies of the introductory promotional materials that you propose to use for this product. Please submit all material in draft or mock-up form rather than final printed format. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

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

Options Under 21 CFR 314.110

Within 10 (ten) days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action, FDA may proceed to withdraw this application as provided for under 21 CFR 314.65. Any amendment should respond to all of the comments and requests in this letter, including those incorporated by reference. We will not process a partial reply as a major amendment, nor will the review clock be reactivated, until all deficiencies have been addressed.

Opportunity for Informal Meeting Under 21 CFR 314.102(d)

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Neuropharmacological Drug Products, to discuss what further steps need to be taken before the application may be approved.

This drug product may not be legally marketed until you have been notified in writing that this application has been approved.

If you have any questions, please 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 (Revised Draft Labeling) [Please note: the electronic signature page will follow the labeling.]

**APPEARS THIS WAY
ON ORIGINAL**

244 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling