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*APPLICATION NUMBER:*

**21-515**

**MEDICAL REVIEW**

**Clinical Review of Safety: NDA 21,515**

**WELLBUTRIN XL Extended-Release Tablets (Bupropion HCl)**

**Sponsor:** GlaxoSmithKline  
**Date of Correspondence:** August 26, 2002  
**Date Received:** August 26, 2002  
**Drug Name:** WELLBUTRIN XL (bupropion HCl extended-release)  
**Drug Class:** Antidepressant  
**Related NDAs & IND:** 18,644, 20,358, IND: 28,676  
**Dosage Strengths:** 150 mg & 300 mg tablets

**I. Overview & Summary of Safety Conclusions**

This review focuses on the safety profile of WELLBUTRIN XL, an extended-release formulation of bupropion, which would be administered once-daily. The safety data reviewed derive from 5 completed bioavailability studies and 3 ongoing efficacy trials using WELLBUTRIN XL. Generally, WELLBUTRIN XL appears to be reasonably safe and well tolerated. The safety profile appears to be quite similar to that of the reference compound, the immediate-release formulation of bupropion. There were no deaths, serious adverse events, or new/unexpected adverse events reported from the 8 trials reviewed. All adverse events associated with WELLBUTRIN XL administration have been included in bupropion labeling.

**II. Introduction and Background**

**A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Group**

The sponsor seeks approval for WELLBUTRIN XL (150 mg and 300 mg tablets), an extended-release formulation of bupropion HCl, for the treatment of Major Depression in adults. The sponsor states that WELLBUTRIN XL has been developed to allow for once-daily dosing, which could enhance convenience, improve compliance, and provide benefits in safety and tolerability compared with BID and TID dosing required during treatment with the immediate and sustained-release formulations of bupropion.

#### **B. Discussions with the Division about the NDA Submission**

On June 11, 2002, the sponsor presented its WELLBUTRIN XL development program to the Division. The Division agreed with the proposal to submit an NDA for WELLBUTRIN XL that would be based on data demonstrating bioequivalence of the extended-release formulation of bupropion and the immediate-release formulation [NDA 18,64], (similar to the submission which formed the basis for approval of WELLBUTRIN SR [NDA 20,358]). The Division requested that the sponsor use Cmax, AUC, and Cmin as primary parameters for determining steady-state bioequivalence and that these be determined for bupropion, hydroxy-bupropion, threohydro-bupropion, and erythrohydro-bupropion. In light of the multiplicity of parameters to be used in the assessment of bioequivalence, an additional measure of bioequivalence, the pharmacological activity-weighted composite (PAWC) of bupropion and its metabolites, was recommended by the Division. This parameter was used for the approval of WELLBUTRIN SR, since > 90% of systemic drug exposure involves metabolites rather than parent drug. In addition, the PAWC was noted by the Division as being potentially important in evaluating bioequivalence if one of the 12 individual parameters to be evaluated differed slightly from those of the reference product.

#### **C. Foreign Marketing History**

No applications for marketing approval of WELLBUTRIN XL have been submitted outside the U.S.

#### **III. Clinically Relevant Findings from Chemistry, Biopharmaceutics**

These will be analyzed and reported by reviewers from the respective disciplines.

#### **IV. Safety Analysis of WELLBUTRIN XL**

##### **A. Description of Clinical Data and Sources**

Safety information reviewed included: 1) individual study reports from the 5 bioavailability studies (2543, 2544, 2548, 2571, and 2526); and 2) case report forms from the 3 ongoing clinical trials using WELLBUTRIN XL. Two of these trials involve treatment of Seasonal Affective Disorder (AK 130930 & AK 130936), and one involves treatment of Attention Deficit Hyperactivity Disorder in Adults (AK 130930).

**B. Exposures, Deaths, SAE, Discontinuations due to AE, and Common AE in the Bioavailability Studies**

In the 5 bioavailability studies, 173 normal subjects were exposed to either single or multiple doses of WELLBUTRIN XL 300 mg for up to 10 days. The total exposure to WELLBUTRIN XL 300 mg was 3.43 patient-years.

There were no deaths, serious adverse events, new or unexpected adverse events compared with adverse events that have been reported and labeled for the bupropion immediate and sustained-release formulations. Discontinuations due to adverse events are described in the table below.

**Table 1. Safety Parameters for the 5 Bioavailability Studies with WELLBUTRIN XL**

	40	40	36	36	21
	30	37	32	35	20
	1.12 pt-years	1.01 pt-years	0.2 pt-years	0.2 pt-years	0.9 pt-years
	None	None	None	None	None
	None	None	None	None	None
	Two: dysuria, urinary urgency  pruritis, rash	One: Pharyngi- tis, fever, leukocy- tosis	Two: swollen hand, arthritis  contusion from venipunc- ture	None	One: Constipa- tion, nausea, bloating

\*Total exposure to WELLBUTRIN XL in the above studies = 3.43 pt-years

In 3 of the 5 studies, the immediate-release formulation of bupropion (300 mg) was used as a comparator. There were no placebo groups for comparison.

The most common adverse events reported during WELLBUTRIN XL administration were: headache, constipation, nausea, abdominal pain or discomfort, rash, tremor, and dizziness. The safety and tolerability profile of WELLBUTRIN XL appears to be quite similar to those of WELLBUTRIN IR and WELLBUTRIN SR. Please refer to the table below.

Table 2. Common Adverse Events in WELLBUTRIN XL Bioavailability Studies

Adverse Event	Wellbutrin XL	Placebo
Headache	9%	11.6%
Constipation	6.7%	13.7%
Nausea	4%	2%
Abdominal pain or discomfort	4%	8.4%
Rash	3.5%	6.3%
Tremor	2%	4.2%
Dizziness	1.6%	5.3%

**C. Safety Data from 3 Ongoing Clinical Trials Using WELLBUTRIN XL**

As of November 19, 2002, there were 604 subjects enrolled in the 3 clinical studies listed in Section IV.A. There have been no deaths or serious adverse events reported from these trials. Nineteen subjects from the SAD studies discontinued due to experiencing adverse events. The cases are described in the table below.

**Discontinuations due to Adverse Events in Ongoing Trials**

Study	Study
allergic reaction	Rash on hands, headache
agitation, headache, and acne	Dizziness, disorientation
facial edema & truncal rash	Hypertension
hypertension	Rash on extremities
shortness of breath, chest pain, insomnia	Fatigue and nightmares
dry mouth, metallic taste, lethargy, impaired concentration, depression	Increased heart rate, decreased concentration, lightheadedness
headache, neck pain, jaw clenching, elevated blood pressure	Menstrual spotting
insomnia	
4 non-serious AEs (illegible from CRF)	
insomnia, anxiety, panic, mental confusion	
acute allergic reaction	
panic attacks	

#### **D. Post-Marketing Experience**

Bupropion has been marketed in the U.S. for depression since 1989. Since that time, over 4 million patients have received bupropion treatment. The sponsor states that no new significant safety concerns have been identified that were not observed in clinical trials using the immediate release formulation of bupropion. Since the extended release formulation of bupropion is not marketed in the U.S. or elsewhere, there have been no spontaneously reported adverse events from post-marketing experiences that have been identified in the GlaxoSmithKline adverse events database.

#### **IV. Conclusions**

- WELLBUTRIN XL appears to be reasonably safe and well tolerated when given to healthy subjects at a dose of 300 mg/day for up to 10 days.
- Limited data on the use of WELLBUTRIN XL in subjects with Seasonal Affective Disorder suggest that there have been no serious or unexpected safety concerns.
- The safety profile of WELLBUTRIN XL appears to be similar to those of WELLBUTRIN IR and WELLBUTRIN SR. No serious, new, or unexpected adverse events have been reported thus far.
- There are some limitations in drawing conclusions about the safety of WELLBUTRIN XL: 1) only a relatively small number of healthy and depressed subjects have been exposed to the drug for fairly short periods; 2) There is very little clinical laboratory and ECG data available for subjects exposed to WELLBUTRIN XL. In most studies, only baseline ECG & clinical laboratory tests were performed.
- We will continue to monitor the safety profile of WELLBUTRIN XL as it is used in ongoing and proposed trials.

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Robert Levin, M.D., February 14, 2003  
Medical Reviewer,  
FDA CDER ODE1 DNDP HFD 120

cc: HFD 120  
T Laughren  
P Andreason  
D Bates

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/s/

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Robert Levin  
2/14/03 12:24:26 PM  
MEDICAL OFFICER

Thomas Laughren  
6/6/03 12:19:34 PM  
MEDICAL OFFICER

I agree that this NDA is approvable; see memo  
to file for more detailed comments.--TPL

## Review of Complete Response to Approvable Letter

**Sponsor:** GlaxoSmithKline  
**Drug:** WELLBUTRIN XL (bupropion extend. release)  
**NDA:** 21-515  
**Material Submitted:** Safety Update; Proposed Labeling  
**Correspondence Date:** June 27, 2003  
**Date Received:** July 3, 2003  
**Drug Category:** Antidepressant  
**Forms available for proposed study:** 150 mg & 300 mg tablets  
**Related NDAs and IND:** 18,644, 20,358, 28,676

### I. Overview and Summary of Safety Conclusions

With this submission, the sponsor has responded to the Division's Approvable Letter dated June 24, 2003. The Division requested that the sponsor provide a safety update, as well as proposed changes to labeling and the patient package insert. This review will focus on the safety update for WELLBUTRIN XL.

The safety update includes safety data from completed and ongoing studies for the period April 2, 2003 through June 6, 2003. The sponsor has provided appropriate data for the safety update regarding six clinical trials. Generally, WELLBUTRIN XL appears to be reasonably safe and well tolerated. During the interval indicated above, there were no deaths. There were 3 serious adverse events, 19 discontinuations due to adverse events, and one pregnancy during the trials. Probably because treatment assignments remain blinded, the sponsor did not submit data regarding commonly reported adverse events for these trials. The sponsor did not provide information about reasons for discontinuation due to adverse events for most of the cases.

### II. Review of Safety Update for WELLBUTRIN XL

#### A. Description of Clinical Data and Sources

The safety information reviewed included summaries of safety findings and narratives of specific cases. There are six relevant studies. One is a bioavailability study (AKBIOVAIL2572), involving 54 healthy subjects, in which the PK profiles of WELLBUTRIN XL and SR were compared. There are two clinical trials comparing the effects on sexual functioning of (300-450mg) and Escitalopram (10-20 mg) in subjects with depression (AK130926 and AK130927). A total of 202 subjects were enrolled as of June 6, 2003. Two trials are studying the efficacy of WELLBUTRIN XL in the prevention of Seasonal Affective Disorder (AK130930 and AK130936). A total of 614 subjects were enrolled as of June 6, 2003. Finally, one trial is assessing the efficacy of WELLBUTRIN XL in adults with Attention-Deficit Hyperactivity Disorder. A total of 162 202 subjects were enrolled as of June 6, 2003.

#### **A. Deaths, SAE, Discontinuations due to AE, and Common AE**

There were no deaths in these studies. There were 3 serious adverse events, 19 discontinuations due to adverse events, and one pregnancy during the trials. Treatment assignments remain blinded, except for in the case of the bioavailability study.

#### **Serious Adverse Events.**

1. (BIOVAIL; bupropion SR for 3 days). Knee pain and swelling. Action: hospitalization, intravenous antibiotics, discontinued from study. Resolved.
2. (AK130936; treatment unknown). Cardiac Arrest in a man with coronary artery disease. He had concomitant treatment with dextroamphetamine. The event occurred after 6 months of study treatment and 10 days after the last dose.
3. He was hospitalized, had stent placed in coronary artery. Resolved.
4. (AK130936; treatment unknown). Appendicitis, requiring appendectomy. The event occurred during the fifth month of study treatment.

#### **Discontinuations due to Adverse Events**

Four occurred in the bioavailability study. The adverse events were rash/urticaria, knee pain and swelling, and two cases of upper respiratory infection. The rash and urticaria resolved upon discontinuing study drug. For the 15 cases in the 5 clinical studies, the specific adverse events leading to discontinuation were not specified. Appendicitis was the reason for one of the cases in Study 936. In studies 926, 927, 930, 936, and 934, there were 4, 7, 0, 2, and 2 discontinuations due to adverse events, respectively. Treatment assignments are unknown.

#### **Pregnancy**

The pregnancy occurred in a 40-year-old woman participating in Study 930. She was exposed to blinded study drug before conception and during the early portion of the first trimester. The outcome is unknown.

#### **Most Commonly Reported Adverse Events**

In AKBIOVAIL2572, subjects had crossover treatment with WELLBUTRIN XL and WELLBUTRIN SR, each for 3 days. During treatment with the XL formulation, 18 of 52 subjects reported adverse events, and during treatment with the SR formulation, 16 of 53 subjects reported adverse events. The most common adverse events were constipation (10% vs. 6%), nausea (6% vs. 4%), and headache (4% vs. 6%). The sponsor did not provide data regarding common adverse events reported in the clinical studies.

#### **IV. Conclusions**

The sponsor has provided an appropriate safety update. Data from this update and the previous update suggest that WELLBUTRIN XL is reasonably safe and well tolerated in adult subjects with Major Depression, Seasonal Affective Disorder, and Attention Deficit-Hyperactivity Disorder. Once the treatment assignments are no longer blinded, it would be useful to have more information about the adverse events reported in these studies.

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Robert Levin, M.D., August 15, 2003  
Reviewer,  
FDA CDER ODE1 DNDP HFD 120

Medical

cc: HFD 120  
T Laughren  
P Andreason  
D Bates

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Robert Levin  
8/15/03 06:28:26 PM  
MEDICAL OFFICER

Thomas Laughren  
8/21/03 01:10:05 PM  
MEDICAL OFFICER  
I agree that this application can now be approved;  
see memo to file.--TPL

**APPEARS THIS WAY  
ON ORIGINAL**