

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-358/S-019**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-358/S-019

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

Dear Mr. Murray:

Please refer to your supplemental new drug application dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin SR (bupropion hydrochloride) Sustained-Release 100 mg and 150 mg Tablets.

We acknowledge receipt of your submission dated March 27, 2001. Your submission of March 27, 2001 constituted a complete response to our February 26, 2001 action letter.

This supplemental new drug application proposes the use of Wellbutrin SR in maintaining an antidepressant effect when dosed up to one year, and provides for changes to the **CLINICAL PHARMACOLOGY-Clinical Trials, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION-Maintenance Treatment** sections of labeling.

We have completed the review of this supplemental new drug application, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on March 27, 2001 (Label Code RL-917). Accordingly, the supplemental new drug application is approved effective on the date of this letter.

Additionally, we note that the final printed labeling submitted on March 27, 2001, only incorporates the changes requested in our Agency letter dated February 26, 2001 when compared to the last approved labeling revision (20-358/S-015; approval date April 10, 2000; Label Code RL-750). Please note that pending supplemental applications 20-358/S-018/S-023 are still under review by the Agency.

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-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

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If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" 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

**CENTER FOR DRUG EVALUATION AND  
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Dear Mr. Murray:

Please refer to your supplemental new drug application dated May 31, 2000, received June 1, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin SR (bupropion hydrochloride) Sustained-Release 100 mg and 150 mg Tablets.

We acknowledge receipt of your submission dated August 10, 2000.

This supplemental new drug application proposes the use of Wellbutrin SR in maintaining an antidepressant effect when dosed up to one year.

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 submit final printed labeling revised as follows:

#### **LABELING**

Under **CLINICAL PHARMACOLOGY-Clinical Trials**,

[The following should be inserted as the final paragraph in this subsection.]

In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on Wellbutrin SR (150 mg bid) were randomized to continuation of their same Wellbutrin SR dose or to placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as a CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final three weeks. Relapse during the double-blind phase was defined as the investigator's judgement that drug treatment was needed for worsening depressive symptoms. Patients receiving continued Wellbutrin SR treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

Under **INDICATIONS AND USAGE**

[The following should replace the final paragraph in this subsection.]

The efficacy of Wellbutrin SR in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial. (see **Clinical Pharmacology**).

Nevertheless, the physician who elects to use Wellbutrin SR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**Under DOSAGE AND ADMINISTRATION-Maintenance Treatment**

[The following paragraph should replace the currently approved language under the **Maintenance** subsection and be retitled **Maintenance Treatment**.]

**Maintenance Treatment**

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In a study in which patients with major depressive disorder, recurrent type who had responded during 8 weeks of acute treatment with Wellbutrin SR were assigned randomly to placebo or to the same dose of Wellbutrin SR (150 mg bid) during 44 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated. (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is unknown whether or not the dose of Wellbutrin SR needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically 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, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental 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 the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

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If you have any questions, call Paul David, R.Ph., 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

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-358/S-019**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## REVIEW AND EVALUATION OF CLINICAL DATA

**NDA:** 20-358  
**Sponsor:** GlaxoWellcome Inc.  
**Drug:** Wellbutrin SR® (bupropion sustained release)  
**Indication:** Treatment of depression-efficacy in the long-term treatment of depression  
**Dates of Submission:** March 28, 2001  
**Materials Reviewed:** Response to approvable letter.

This review summarizes the sponsor's response to the Division's approvable letter.

The sponsor has agreed to the Division's draft labeling changes with only one minor stylistic change. The sponsor proposes using the phrase "twice-a-day" in lieu of BID. This is acceptable.

### Conclusions/Recommendations

This submission constitutes a complete response to the Division's approvable letter and the proposed change is acceptable. I recommend that the Division approve supplement SE1-019 with this version of proposed labeling.

Paul J. Andreason, M.D.  
Medical Review Officer, DNDP

cc: NDA 20-358  
HFD-120  
HFD-120/ P Andreason  
P David  
R Katz  
T Laughren

## REVIEW AND EVALUATION OF CLINICAL DATA

**NDA:** 20-358  
**Sponsor:** GlaxoWellcome Inc.  
**Drug:** Wellbutrin SR® (bupropion sustained release)  
**Indication:** Treatment of depression-efficacy in the long-term treatment of depression  
**Dates of Submission:** May 31, 2000  
**Materials Reviewed:** SNDA SE1-019

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## 1.0 Material Utilized in Review

### 1.1 Materials from NDA/IND

The following items were examined during the course of this clinical review:

<b>DATE</b>	<b>DESCRIPTION</b>
May 31, 2000	NDA efficacy supplement 20-358 SE1-019

CRF's for patients 3382, 3388, 4015, 4179, 4607, and 4781 were audited.

### 1.2 Related Reviews

Original NDA review 20-358.

## 2.0 Background

### 2.1 Indication

Bupropion sustained release formulation (BSR) is indicated for the treatment of depression and smoking cessation. BSR was studied in depressed patients who most closely resemble patients with major depressive disorder as defined by the DSM-IV. BSR is marketed as Wellbutrin SR for the treatment of depression and as Zyban for the treatment of smoking cessation.

### 2.2 Related INDs and NDAs

[REDACTED] NDA 18-644 is for the immediate release formulation of bupropion HCl. Zyban, (BSR under another name) is NDA 20-711.

### 2.3 Administrative History

An immediate release (IR) formulation of **WELLBUTRIN** was approved in 1989 for marketing in the US for the treatment of depression. A sustained release formulation of **WELLBUTRIN (WELLBUTRIN SR)** was approved in 1996 for the treatment of depression. **ZYBAN**, NDA 20-711 was approved in May 1997 for the treatment of smoking cessation.

### 2.4 Directions for Use

The usual target dose for BSR for both depression and smoking cessation is 150-mg PO BID. Administration of BSR should be done so as to minimize the risk of seizure. To help prevent seizures, it is recommended that single doses not exceed 200-mg, that doses are separated by at least eight hours, and that doses not exceed a daily total of 400-mg. BSR is also contraindicated for patients with a history of seizures or eating disorders. The sponsor recommends initiating drug therapy at 150-mg PO qam for at least the first four days of treatment. If this is well tolerated the dose should be increased to 150-mg PO BID. Doses of up to 200-mg PO BID may be used for depression.

Blood pressure monitoring is recommended for patients using BSR in combination with a nicotine patch; however, no recommendations are given for monitoring blood pressure

for BSR monotherapy. There are no specific laboratory tests recommended for patients taking BSR.

### 3.0 Chemistry

There are no chemistry issues to review in this submission.

### 4.0 Animal Pharmacology

There are no animal pharmacology/toxicology issues to review in this submission.

## 5.0 Description of Clinical Data Source

### 5.1 Extent of exposure

Protocol No	Study Design	Study Drug Dose, Route, Duration	N
AK1A-4004	Multi-center, randomized (1:1), parallel group, placebo controlled, fixed dose, time to relapse design	Bupropion sustained release 150-mg PO BID, 8-weeks open -label, 44-weeks double blind	417 207 BSR 210 PBO

The extent of exposure of patients in study 4004 to BSR follows in table 5.3.1 and 5.3.2.

Treat group and phase	N	Patient- days	Patient- years
WSR Open- label	816	37,173	101.84
Placebo Double- Blind	213	24,696	67.66
WSR Double- Blind	210	30,640	83.95

Exposure time (days)	Numbers of patients who took an average daily dose in this range (based on pill count)			
	150 - < 200 mg	200 - < 250 mg	250 - < 300 mg	>= 300mg
Start of Study				
56 < day <= 63	0	0	2	3
63 < day <= 70	0	0	11	6
70 < day <= 84	0	0	14	6
84 < day <= 98	0	0	12	3
98 < day <= 112	0	0	11	7
112 < day <= 140	0	1	12	8
140 < day <= 168	1	2	12	1
168 < day <= 196	0	1	10	3
196 < day <= 224	0	0	5	0
224 < day <= 252	0	0	4	3
252 < day <= 280	0	0	2	0
280 < day <= 308	0	0	3	0
308 < day <= 336	0	0	3	1
336 < day <= 364	0	1	25	3
day > 364	0	1	32	1

## **5.2 Adequacy of Clinical Experience**

The study is well designed and adequately controlled. Short-term studies demonstrate that BSR is effective in the short-term treatment of major depression. Therefore, one study is adequate to support the claim of extended efficacy for BSR.

## **5.3 Data Quality and Completeness**

The data appears to be complete with few inconsistencies. One inconsistency was for patient 4015 who was listed in the submission as dropping out due to elevated liver enzymes; however, after review of the CRF, it appears that the patients was discontinued because of pregnancy.

## **6.0 Human Pharmacokinetics**

There are no human pharmacokinetic issues to review with this submission.

## **7.0 Review of studies for which efficacy claims are made**

### **7.1.1 Investigators and Sites**

This was a 22 site, US based study. Principal investigators with the number of patients in the double blind phase for each investigator are listed in the appendix in table 7.1.1.

### **7.1.2 Objectives**

The primary objective of this study was to evaluate the efficacy of BSR compared to placebo for the prevention of relapse/recurrence of depression in subjects previously shown to respond to BSR as measured by time to relapse/recurrence of depression. The secondary objectives of this study were to assess safety, quality of life, productivity, and resource use over time for subjects who received BSR versus those who received placebo.

### **7.1.3 Study Population**

Patients in this study suffered from major depression and experienced clinical relief with BSR. Patients that were eligible for enrollment in this study had to have a diagnosis of Recurrent Major Depression as defined in *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM - IV)*, and a minimum score of 18 on the 21-item Hamilton Depression Scale (HAMD). Outpatients who satisfied these screening requirements entered an 8-week Open-Label Phase with BSR 300mg/day. A sufficient number of subjects were to be enrolled in the open-label phase to provide approximately 400 subjects who were qualified to enter the double-blind phase because they: 1) responded to treatment as defined by a clinical global impressions scale of improvement (CGI-I) rating of "1" or "2" for the last three consecutive weeks (weeks 6, 7, and 8) of the open-label phase of the study and 2) agreed to enter the 44-week, placebo-controlled double-blind phase. Subjects who entered the double-blind phase were to be randomized (1:1) to either BSR 300mg/day (150mg b.i.d.) or placebo (approximately 200 subjects for each group).

### **7.1.4 Design**

This was a multicenter, parallel, randomized, fixed dose, double blind, and placebo-controlled, time-to-relapse design trial in outpatients diagnosed with recurrent major depression. The study lasted up to 53 weeks and consisted of three phases: Screen Phase (1-week duration), open-label Phase (8 weeks duration), and double blind phase (44

weeks duration). After giving informed consent, completing screening assessments, and meeting inclusion/exclusion criteria, all subjects entered a 1-week screening phase. Following completion of the screening phase, those subjects who continued to satisfy the inclusion/exclusion criteria requirements were enrolled in the open-label phase. Clinic visits were conducted weekly during the 8-week open-label phase. Subjects whose depression responded to treatment during the open-label phase (defined as a CGI-I rating of 1 or 2 at each of the last 3 visits, namely Weeks 6, 7, and 8) were randomized to either BSR 150-mg PO BID or placebo in the double blind phase. Clinic visits were conducted at Weeks 9, 10, 12, 14, 16, and every 4 weeks thereafter through Week 52. The primary efficacy measure of the study was time to relapse/recurrence of depression in the double blind Phase. In the analysis, time to relapse/recurrence was to be measured using the time from entry into the double blind phase to prescription of pharmacotherapy or ECT as judged by the investigator to be necessary for the treatment of depression.

#### **7.1.5 Assessments**

Table 7.1.5.1 in the appendix outlines the assessment instruments and their respective schedules of administration for the screening, baseline, and double blind phases of the protocol.

#### **7.1.6 Analysis Plan**

##### **Primary Efficacy Variable**

The primary objective of this study was to evaluate the efficacy of BSR compared to placebo for the prevention of relapse/recurrence of depression in subjects previously shown to respond to BSR as measured by time to relapse/recurrence of depression. Survival analysis methods were used to compare the two treatment groups with regard to time to relapse/recurrence of depression as defined by the time from entry into the double blind phase to prescription of pharmacotherapy or ECT as judged by the investigator to be necessary for the treatment of depression. The primary analysis used the Wilcoxon test to compare the survival curves for the two treatment groups. Subjects who were discontinued from the study without a date of prescription for pharmacotherapy or ECT were considered censored observations at the time of study discontinuation, as were those subjects who completed the trial without relapse/recurrence of depression.

##### **Secondary Efficacy Variables**

The following efficacy analyses were performed on the safety population.

- HAMD total score (calculated as the mean of the non-missing items of the 21-item HAMD multiplied by 21)
- HAMD Depressed Mood score (item number 1) HAMA total score (calculated as the mean of the non-missing items of the 14-item HAMA multiplied by 14)
- CGI-S rating
- CGI-I rating

For each variable, two scores were computed at each visit: an observed score and an LOCF score. In addition, at each visit following Day 0 (Baseline), the change from the baseline value in the absolute score was computed for each score (observed and LOCF) with the exception of CGI-I, where there was no baseline value. Four scores were available for each variable (except CGI-I), for each subject, at each visit.

#### **7.1.7 Patient Disposition**

Totals of 1011 patients from 22 centers gave written informed consent before the initiation of any study procedures and were screened for the study. Of these patients, 183 were discontinued from the study during the screening phase. Of the 828 patients enrolled in the open-label phase, 310 (37%) did not complete this phase. Of the 518 remaining patients, 95 completed the open-label phase but did not enter the double blind phase.

Among these 95 patients who completed the open-label phase 4 dropped out due to adverse events, and 17 withdrew consent. The remaining 73 were considered “inappropriate for randomization”.

Of the 95 patients who completed the open-label phase, there was a subset of 25 patients whom the investigator indicated had responded based on the CGI-I criteria, but who did not enter the double-blind phase because they were not eligible for other reasons (n = 6) or withdrew consent (n = 15) or were discontinued for an adverse event (n = 4). These patients (n = 25) plus those who entered the double-blind phase (n = 423) were classified as responders for open-label phase psychometrics analyses (n = 448).

The 423 eligible patients who entered the double blind phase were randomized as follows: BSR (n= 210) and placebo (n = 213). Table 7.1.7.1 enumerates the disposition of these patients in study 4004. Patients who completed the protocol are those who did not require pharmacological intervention (no patients went on to receive ECT immediately after dropping out) beyond the study drug. The term “condition deteriorated” means that patients experienced a relapse/recurrence.

<b>Table 7.1.7.1 Disposition of patients in the double blind treatment phase of study 4004</b>		
<b>Reason</b>	<b>Placebo N=213 n= (%)</b>	<b>BSR N=210 n= (%)</b>
Protocol complete	43 (20)	60 (28)
Adverse Events	2 (1)	8 (4)
Condition Deteriorated	100 (47)	71 (34)
Lost to follow-up	21 (10)	16 (8)
Consent Withdrawn	31 (15)	36 (17)
Protocol Violation	15 (7)	19 (9)
Other	1 (1)	0

### **7.1.8 Baseline Demographics/Severity of Illness**

Treatment groups in the double blind phase were similar with respect to sex, age, physical characteristics, and ethnic origin. Females comprised 66% and 64% of the BSR and placebo treatment groups, respectively. Most subjects in both treatment groups (approximately 87%) were Caucasian. Mean age was 39 years in the BSR treatment group and 40 years in the placebo treatment group. The psychiatric history profile of subjects enrolled in the two treatment groups was similar. More than 75% of the subjects in both treatment groups were classified as moderately depressed (range: 78% - 84%). A substantial percentage of subjects in both treatment groups had 5 or more previous episodes (range: 28% - 31%). Approximately 50% had been depressed for 2-6 months prior to Screen (range: 50% - 56%).

### **7.1.9 Concomitant Medications**

A similar percentage of subjects in both treatment groups (79% BSR and 82% placebo) were taking at least one concurrent medication during the double blind phase. In addition, a similar number of patients began taking a concomitant medication during the double blind phase (47% of BSR - compared to 41% of placebo-treated subjects). The types of concomitant medications used and the rates at which they were used were similar except for diphenhydramine, which was used more often in the placebo group (5%) than in the BSR group (1%).

### **7.1.10 Efficacy Results**

The primary efficacy variable in the study was the time to relapse/recurrence of depression as measured by the time between initiation of double-blind medication and the first prescription of pharmacotherapy or ECT (time to intervention). No subject was prescribed ECT to treat relapse/recurrence of depression.

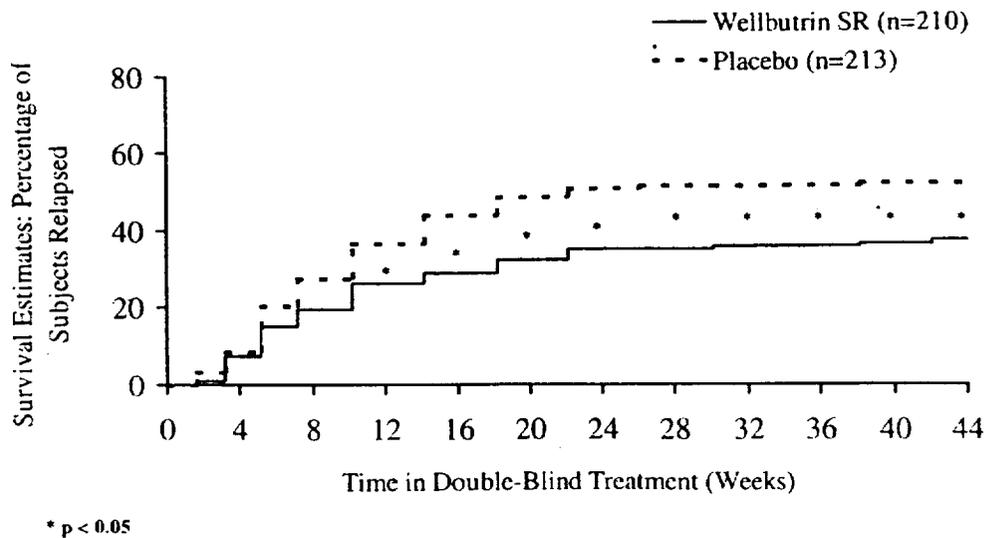
A total of 31 BSR-treated subjects experienced a relapse of their index episode of depression while 42 placebo-treated subjects experienced a relapse. Depression that was severe enough to require pharmacologic intervention or ECT (a recurrence), emerged in 40 and 58 subjects in the BSR and placebo treatment groups, respectively, over the course of the last nine months of the study.

The main survival analysis censored observations at the time of a subject's study discontinuation. A statistically significant difference in favor of BSR was seen when the survival curves for the two treatments groups were compared using both the Wilcoxon ( $p=0.0041$ ), and log-rank ( $p=0.0028$ ) tests. Subgroup analysis was performed based on age, sex, and ethnic origin. Results of survival analysis for men were  $p=0.0434$  and  $p=0.0548$  on the Wilcoxon and log-rank tests, respectively; for women, results on the Wilcoxon and log-rank tests were  $p=0.0377$  and  $p=0.0203$ , respectively. Subgroup sample sizes for white versus non-white and age were too small to draw meaningful conclusions.

The difference between treatment groups with respect to time-to-relapse is illustrated in figure 7.1.10.1 below.

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**Figure 7.1.10.1 Time to Relapse/Recurrence of Depression in Study 4004**



### 7.1.11 Conclusions

The results and analysis of Study 4004 support a claim for maintenance of treatment effect with continued therapy.

## 8.0 Safety

### 8.1.1 Deaths in Study

One patient died during the study. Patient 5192, a 34 year-old taking BSR 150-mg BID for 25 weeks, died after 15-days in the hospital due to injuries sustained in a boating accident. It is unlikely that this death was drug related. This occurred during the double blind phase. There were no deaths during any other part of the study.

### 8.1.2 Serious Adverse Events

Nine subjects reported serious adverse events in the open-label phase. Seven of the nine were unlikely to be connected with drug treatment.

On Day 25, patient 4120 a 42 year-old woman experienced an “anaphylactic reaction”, was hospitalized, and was discontinued from the study. The patient had a history of asthma and had an anaphylactic reaction at 2 years of age. The study drug was stopped after the patient was hospitalized; however, the patient did not receive BSR again. Though allergic reactions to BSR have been documented one can not necessarily conclude that this patient’s experience was connected to BSR. Whether this case is drug related or not, labeling for BSR contains language that indicates that patients may have experienced drug-related allergic or serum-sickness like syndromes.

On Day 44, Subject 3388 experienced a “grand mal seizure” and was discontinued from the study. She admitted snorting amphetamines and also using oral **RIPPED FUEL**, a body building supplement containing MaHuang extract (standardized for 6% ephedrine) and guarana extract (standardized from 22% caffeine). BSR is clearly labeled as a drug that may increase the risk of seizure in a dose dependent fashion. It is likely that BSR may have contributed to this event but it is also highly likely that if the patient had followed protocol that this event would not have occurred.

Eleven patients experienced 15 serious adverse events during the double blind treatment phase. Eight of the patients were taking BSR and three were taking placebo. None of these events were likely to be drug related. None of the placebo related events were likely to be related to stopping BSR. Brief descriptions of the patients who experienced these adverse events may be found in the appendix in table 8.1.2.1.

### **8.1.3 Dropouts due to Adverse Events**

Eight BSR treated patients who dropped out due to adverse events versus two placebo treated patients in the double blind phase. Patient 4015 is discussed in section 8.1.6.2. Though patient 4015 ostensibly dropped out due to (mildly) elevated liver enzymes, the CRF investigator’s comments states that she reported that she became pregnant.

Subject 4781 (BSR), a 23-year-old female with a baseline BMI of 20 was discontinued in the double-blind phase for weight loss. According to the CRF she refused the end-of-study evaluation because of lack of time. The subject met criteria for clinically significant weight loss beginning at Day 168, having lost 15.2 pounds (13.4% of Baseline weight). At the last visit, Day 196, the subject had lost 17.2 pounds (15.2% of Baseline weight). No other subjects were discontinued for any weight change adverse events. It is unclear if there was any relationship to BSR.

Subject 3388 is discussed above in section 8.1.2

CRF’s for the other dropouts were reviewed and there were no events that were likely to be drug related among these patients. A line listing of patients who dropped out due to adverse events may be found in the appendix in table 8.1.3.1.

### **8.1.4 Specific Search Strategies**

None

### **8.1.5 Adverse Events**

There were two events that met criteria for common and drug related ( $\geq 5\%$  and at least twice placebo) between the treatment groups during the double blind phase. These events were infection (10% BSR and 5% PBO) and urinary tract infection (5% BSR and 0% PBO). There were no remarkable shifts from normal to low neutrophil counts in BSR treated patients in relation to placebo treated patients at either week 8, 24 or 52. One BSR treated patient was hospitalized to treat influenza. These are more than likely spurious findings and need not be added to labeling.

### **8.1.6 Laboratory Findings**

#### **8.1.6.1 Analysis of Central Tendency**

There were no analyses of mean or median changes in laboratory values.

### 8.1.6.2 Analysis of Outliers

Tabulations of normal and “expanded normal” (potentially clinically significant) are listed in the appendix in tables 8.1.6.2.1 and 8.1.6.2.2. The sponsor examined the laboratory data to see how many patients shifted from normal to high or low values as well as normal to potentially clinically significant. This section discusses the shifts from normal to outside of normal and “expanded normal” (potentially clinically significant) ranges.

On visual inspection, the double blind phase shift data showed no marked or unbalanced numbers of patients who shifted from normal to abnormal ranges except for blood glucose. The following table enumerates the percentage of patients shifting from normal values for glucose.

	Planned Relative Time	Shift Category	Placebo (n=213)		Wellbutrin SR (n=210)	
Glucose (mg/ dL)	Week 24	To Low	6/60	(10%)	3/ 91	(3%)
		To Normal or No Change	50/60	(83%)	84/ 91	(92%)
		To High	4/60	(7%)	4/ 91	(4%)
	Week 52	To Low	4/ 126	(3%)	6/ 118	(5%)
		To Normal or No Change	114/ 126	(90%)	98/ 118	(83%)
		To High	8/ 126	(6%)	14/ 118	(12%)

There are two shifts that appear unbalanced. At week 24, 10 % of placebo patients had shifted from normal to low with only 3% of BSR treated patients. At Week 52 12% BSR patients shifted from normal to high. At week 24 relatively fewer BSR patients had shifted from normal to high glucose values at week 52 relatively more BSR patients had shifted from normal to high glucose values.

At this point few conclusions can be drawn from these observations. For some added perspective, there are only 17 reported cases of hyperglycemia in the AERS database for Wellbutrin since February of 1991. Ten of these cases described patients with diabetes, carcinoma, lupus, or multiple drug overdoses. There were 7 reports of hyperglycemia with no concomitant medications, but all had scant information or glucose values. None reported hospitalization or “treatment emergent diabetes”. Additionally, a search of the literature revealed no references to bupropion in association with hyperglycemia. Therefore these two apparent imbalances in shift from normal range are most likely due to chance.

One patient discontinued the study for an abnormal laboratory value and is described below. Another patient had a mysterious and marked elevation in blood glucose that is also described below. These two cases as well as other PCS elevations were unlikely to be drug related.

One patient discontinued the study for elevated liver enzymes. According to the summary in the submission, subject 4015 (BSR) was prematurely discontinued due to elevations in hepatic enzymes; however, the CRF states that she reported that she was pregnant on 11/24/98. She informed the investigator that she wished to continue BSR and that her private doctor stated that it would be okay for her to do so. This subject, a 22 year-old female, was discontinued after 69 days on medication (55 days in the open-label Phase and 14 days in double blind phase). The ALT and AST values over time are shown in the appendix in table 8.1.2.6.4. This subject's laboratory values were decreasing at the time of discontinuation. It is therefore unlikely that this event was drug related.

Patient 3501 had a blood-glucose of 432-mg% at day 56 (end of treatment in open label phase). This patient was randomized to placebo and on repeat testing had a glucose value of 97-mg%. The patient did not discontinue the study and did not have elevated levels for the remainder of the study. There were no reported symptoms. To gain some perspective on this case, a search of the AERS database was performed. There are 17 reported cases of hyperglycemia in the AERS database for Wellbutrin since February of 1991. Ten of these cases described patients with diabetes, carcinoma, lupus, or multiple drug overdoses. There were 7 reports of hyperglycemia with no concomitant medications, but all had scant information or glucose values. None reported hospitalization or "treatment emergent diabetes". Given the lack of reported symptoms with this glucose level, one might entertain the possibility of laboratory error. In any case, based on the large experience with BSR it is unlikely that this event was drug related.

### **8.1.7 Vital Signs**

BSR labeling recommends that patients' blood pressure be monitored if they are concurrently using a nicotine patch. This recommendation is based on several reported cases of hypertension associated with the concomitant use of BSR and nicotine replacement products for the cessation of smoking. The sponsor is currently studying the effect of BSR alone in patients who have borderline yet untreated hypertension. This review of vital signs is made with an eye to this issue as well general screening.

#### **8.1.7.1 Analysis of Central Tendency**

There were no mean changes in vital signs and weight that were likely to be drug related or of clinical significance.

Mean systolic blood pressure was 120.7mmHg at baseline and 120.1mmHg at Day 56 for open-label phase subjects. In the double-blind phase, it was similar in the two treatment groups at baseline at 120.7 and 119.1mmHg for the BSR and placebo treatment groups, respectively. At discontinuation, the observed means were 125.3 and 124.8mmHg for the two respective treatment groups. Mean diastolic blood pressure was 77.5mmHg at baseline and 77.8mmHg at Day 56 for open-label phase subjects. In the double-blind phase, it was similar among the two treatment groups at baseline at 78.1 and 77.0mmHg for the BSR and placebo treatment groups, respectively. At discontinuation, the observed means were 79.6 and 81.7mmHg for the two respective treatment groups. No mean change in either systolic or diastolic blood pressure was noted in longer-term treatment.

The mean observed pulse rate was 75.7 beats per minute (bpm) at baseline and 78.1 bpm at Day 56 for Open-Label Phase subjects. In the double-blind phase, it was similar in the two treatment groups at Baseline at 75.6 and 76.0 bpm for the BSR and placebo treatment groups, respectively. At discontinuation, the observed mean was 78.9 and 76.7 bpm for the two respective treatment groups. These mean changes are not clinically significant.

Mean weight was 81.0kg at baseline and 80.8kg at Day 56 for open-label phase subjects. In the double blind phase, it was similar in the two treatment groups at Baseline at 83.1 and 82.4kg for the BSR and placebo treatment groups, respectively. At discontinuation, the observed means were 86.0 and 85.7kg for the two respective treatment groups. The sponsor noted that several subjects at one site (Investigator # 44506/Croft) had relatively sizeable changes in weight between study visits. The scale used to measure weight at the site was changed three times in the early part of the study. The first scale was used until approximately the second week of March 1998, the interim scale was used from that point onwards until April and use of the third scale, which was utilized for the remainder of the study, began April 14, 1998. The site noted these changes in the Investigator Comment Log. No data from these subjects were excluded. These results show roughly a 5-kg weight gain over the duration of the study regardless of treatment group. Though 5-kg could represent a remarkable mean increase in weight, it is unlikely to be drug related.

#### **8.1.7.2 Analysis of Outliers**

Table 8.1.7.2.1 lists the criteria for potentially clinically significant changes in vital signs and weight. There were 18 subjects in the open-label phase and 10 subjects (5 BSR and 5 placebo) in the double-blind phase whose readings met criteria. There were 13 subjects in the open-label phase that met criteria for a clinically significant change in systolic blood pressure; for 12 of 13 subjects, criteria were met for only one visit. For all 13 subjects, the nature of the change was a decrease. In the double-blind phase, three BSR and four placebo subjects met criteria for a clinically significant change in systolic blood pressure. Criteria were met for only one visit for two of the three BSR -treated subjects and for two of the four placebo-treated subjects. For these 7 subjects (3 BSR and 4 placebo), the nature of the change was a decrease. Criteria were met for a clinically significant change in diastolic blood pressure at only one visit for both of the two BSR -treated subjects who met criteria; the one placebo-treated subject met criteria for two non-consecutive visits. For all 3 subjects (2 BSR and 1 placebo), the nature of the change was an increase.

The following three cases represent increases in blood pressure.

Subject 4656 (open label) was discontinued from the open-label phase due to elevated blood pressure. The subject had a blood pressure of 154/90mmHg at screening, and 160/94mmHg at baseline. Trial medication began 07 May 1998 and was discontinued 11 May 1998. The onset date of the adverse event was 09 May 1998; there is no blood pressure reading available for this date as it fell between study visits. At the discontinuation visit, conducted 14 May 1998, the blood pressure reading was 150/100mmHg. The investigator indicated that the adverse event had a reasonable possibility of being caused by the trial medication. No other subjects were discontinued for changes in blood pressure.

Subject 3941 (BSR), a 37 year-old male (height = 175cm), met criteria for a clinically significant change in diastolic blood pressure (150/107) at one open-label phase visit (Day 42). His screening and baseline blood pressures were 130/64 and 132/66. Diastolic blood pressures were 101-107 mmHg from days 21 through 42. The patient was continued in the study for 36 weeks. Weeks 16 and 24 visits show blood pressures of 132/93 and 128/98 mmHg. All other diastolic blood pressures were 90-mmHg or below. The subject discontinued at week 36 due to the recurrence of depression. It is unclear if BSR had any association with this patient's intermittent borderline hypertension.

Subject 4500 (BSR), a 49 year-old female (height = 179cm) met criteria for a clinically significant change in systolic blood pressure at one double-blind phase visit (Week 28). In addition, her Week 36 blood pressure was 196/114 mmHg. Her screening blood pressure was 160/100. This patient remained in the study for 52 weeks. Weeks 44-52 blood pressures were normal (126/88-134/62 mmHg). It is unlikely that this patient's hypertension was related to BSR.

Analysis of these outliers do not point to drug related increases in either systolic or diastolic blood pressures.

#### **8.1.8 ECG Findings**

No ECGs were performed in this study.

#### **8.2 Adequacy of patient exposure and safety assessments**

BSR is marketed as Wellbutrin SR and Zyban. There is a vast clinical experience with BSR so that most of its potential safety problems are known. Currently the Division has asked the sponsor to look into two safety concerns- a potential drug interaction with warfarin and a potential increased risk for hypertension. The study in this submission was not designed to address either of these issues. No coagulation studies were performed and no patients were taking warfarin in this study. Vital signs, on the other hand, were systematically reviewed.

Analysis of central tendency and outlier analysis failed to reveal a signal for an increased risk of hypertension when comparing BSR with placebo in patients with depression. Labeling for BSR currently states that physicians should monitor blood pressure in patients using BSR and nicotine patches concomitantly. Though this study fails to reveal any signal for an increased risk of hypertension in patients using BSR alone, it was not primarily designed to answer this question. The sponsor is currently studying the effects of BSR used without a nicotine patch versus placebo in patients with borderline high yet untreated hypertension.

Though there are outstanding questions as to the effects of bupropion monotherapy on blood pressure, labeling changes suggesting monitoring that is greater than medically suggested for other antidepressant treatments is not necessary at this point.

Patient exposure in this study and the premarketing development program are adequate to support the long term use of Wellbutrin SR as safe when used within the labeled limits.

### **9.0 Labeling Review**

The sponsor proposes changes to the CLINICAL TRIALS, INDICATIONS AND USAGE sections and the **Maintenance** subsection of the Dosage and administration section. I suggest that terms referring to relapse be replaced by "maintenance of effect". The statement that BSR was equally effective for men and women is potentially misleading. Though a subgroup analysis showed no group related treatment difference by sex with respect to rate of dropout, this does not necessarily imply equal effectiveness in a broad sense.

Draft labeling follows in the appendix.

### **10.0 Conclusions**

The results and analysis of Study 4004 support a claim that WELLBUTRIN SR treatment efficacy is maintained with extended treatment for up to 44 weeks following 8 weeks of successful open-label acute treatment (52 weeks total) at a dose of 300 mg/day. This study revealed no new unlabeled safety concerns.

### **11.0 Recommendations**

I recommend an approvable action for supplement SE1-019.

Paul J. Andreason, M.D.  
Medical Review Officer, DNDP

cc: NDA 20-592  
HFD-120  
HFD-120/ P Andreason  
P David  
R Katz  
T Laughren

## Appendix

<b>Table 7.1.1 Investigators and Sites in Study</b>	
Robert Bielski , M.D (25)	Alan J. Cohen, M.D.(3)
Charles Coleman, M.D.(36)	Harry Croft, M.D.(26)
Lynn Cunningham, M.D.(8)	Daniel Dansak, M.D (10)
G. Michael Dempsey, M.D.(24)	Eugene DuBoff, M.D. (23)
David Dunner, M.D.(3)	Louis Fabre, M.D., Ph.D. (23)
Jon Heiser, M.D. (9)	Luis Herrero, M.D. (27)
James W. Jefferson, M.D. (PI changed to Rise Futterer, M.D. effective 1/18/99) (8)	Edmund Settle, Jr., M.D. (PI changed to Sidney Lerfald, M.D. effective 6/26/98)(31)
Peter Londborg, M.D. (22)	Bruce Lydiard, M.D., Ph.D. (7)
Robert Moreines, M.D. (16)	Robert Riesenber, M.D. (26)
Harold Udelman, M.D. (42)	Karen Weihs, M.D. (23)
Kimberly Yonkers, M.D. (PI changed to Rege Stewart, M.D. effective 8/16/99) (12)	Sidney Zisook, M.D (19)

**Table 7.1.5.1 Time and Events Schedule for Study AK1A-4004**

	Screen/ Baseline		Double Blind Treatment Phase													
	-1	0	9	10	12	14	16	20	24	28	32	36	40	44	48	52
(Study Week)	-1	0	9	10	12	14	16	20	24	28	32	36	40	44	48	52
(Event Study Day)	-6	0	63	70	84	98	112	140	168	196	224	252	280	308	336	364
Informed Consent	X															
Inclusion/ Exclusion	X	X														
Medical History	X															
Physical Examination	X															
Laboratory Assessment	X								X							X
Pregnancy Test	X															
Demographics	X															
Smoking History Assessment		X			X				X			X				X
Psychiatric History	X															
History of Mood Disorder (SCID)	X															
21- item HAMD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAMA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI- S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI- I			X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAAST Questionnaire	X															
Vital Signs/ Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experiences		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Medication Record		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life (QLDS)		X			X				X			X				X
Productivity		X			X				X			X				X
Resource Use		X			X				X			X				X
Discontinuation																X

**Table 8.1.2.1 Brief Summaries of Patients with Serious Adverse Events that were Unlikely to be Drug Related in the Open Label Phase**

- On Day 4, Subject 4739 took an overdose (17 150mg tablets) of WELLBUTRIN SR which was characterized as an “attempted suicide;” she was discontinued from the study.
- On Day 31, Subject 4014 reported removal of four tumors from his skin. He remained in the study, and the investigator indicated that “recurrent skin cancer” did not have a reasonable possibility of being caused by the study drug.
- On Day 32, Subject 4583 was hospitalized due to a “fractured arm resulting from a motor vehicle accident.” The subject had stopped taking study medication on her own one day prior to the accident.
- On Day 26, Subject 4588 was hospitalized for “tympanic membrane perforation secondary to acute otitis media.” She continued taking study medication.
- On Day 46, Subject 4288 was “stabbed” during a robbery attempt at an ATM. She was discontinued from the study.
- On Day 16, Subject 4432 experienced “chest discomfort” and was discontinued from the study.
- On Day 47, Subject 4208 experienced “despondence” and attempted suicide. Study medication was discontinued.

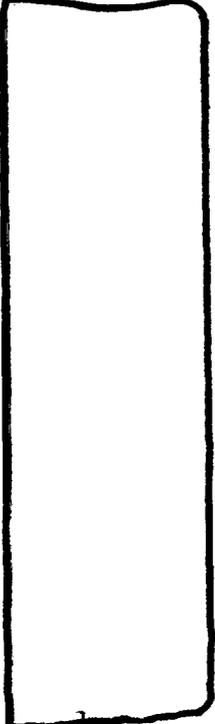
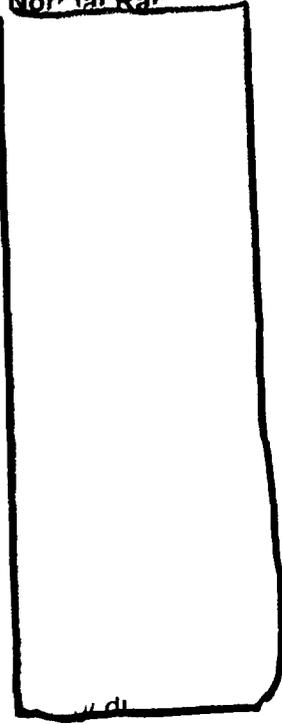
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**Appendix 8.1.2.2 Brief Summaries of Patients with Serious Adverse Events that were Unlikely to be Drug Related in the Double Blind Phase**

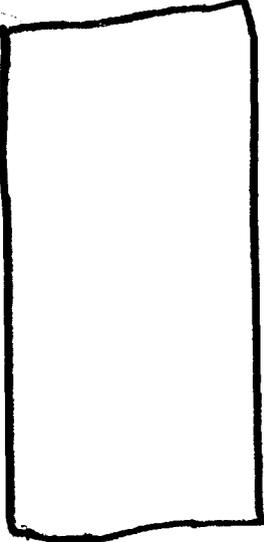
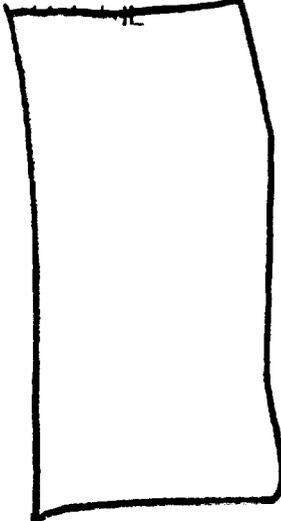
- On Day 212, Subject 3657 (WELLBUTRIN SR) was diagnosed with “coronary artery disorder.” The subject was discontinued from the study because of the circumstances surrounding the hospitalization and treatment, but not because of the medical nature of the SAE.
- On Day 165, Subject 3492 (WELLBUTRIN SR) was “stabbed” during a robbery attempt. The subject remained in the study after a temporary interruption of study medication.
- On Day 173, Subject 5192 (WELLBUTRIN SR) was fatally injured in a “boating accident”.
- On Day 321, Subject 4411 (placebo) experienced a “rectal hemorrhage.” Study medication was not discontinued.
- On Day 85, Subject 5003 (WELLBUTRIN SR) experienced “cholecystitis,” and on Day 107 “pancreatitis.” Study medication was not discontinued.
- On Day 168, Subject 3583 (WELLBUTRIN SR) was hospitalized to treat “influenza.” She was discontinued from the study.
- On Day 92, Subject 3533 (WELLBUTRIN SR) was discontinued from the study due to pregnancy. She experienced a “spontaneous abortion” in the first trimester.
- On Day 79, Subject 3390 (placebo) experienced the onset of what was later diagnosed as “myasthenia gravis” and was later discontinued from the study.
- On Day 60, Subject 3445 (WELLBUTRIN SR) experienced the onset of “postmenopausal bleeding.” On Day 117, the patient was diagnosed with “uterine leiomyoma” and was hospitalized for surgery. Study medication was not discontinued.
- On Day 66, Subject 3424 (placebo) developed an “inguinal hernia” which required surgery. Study medication was temporarily interrupted, but the subject continued in the study. As noted in the Open-Label Phase section. Subject 3424 experienced the onset of cholelithiasis” on Day 31. On Day 170, the subject was diagnosed with “cholecystitis,” as well as the cholelithiasis. Study medication was temporarily interrupted to treat these events, but the subject continued in the study.
- On Day 63, Subject 5001 (WELLBUTRIN SR) was diagnosed with “renal calculus” which required surgical removal. Study medication was not discontinued.

Table 8.1.3.1 Listing of Adverse Dropouts in the Double Blind Phase of Study 4004					
Treatment Group	Subj.	Reason for Discontinuation	Adverse Event (raw term)	Onset of Event (day)	Day of Last Dose
Placebo	3390	Hospitalized and later diagnosed with Myasthenia Gravis. KAH	Myasthenia Gravis	79	84
	3637	Hypomania	Hypomania	78	85
BSR	3382	Experienced hives	Hives	72	73
	3583	Discontinued medications due to hospitalization for the flu	Flu.	173	173
	4015	Pt had elevated liver enzymes. Pt was discontinued/ (also pregnant by CRF)	Elevated liver enzymes	55	69
	4179	AE of chest pain of unknown etiology	Chest pain - intermittent	257	285
	4579	Pt c/ o chest pain, pt discontinued as precautionary measure	Chest pain	155	156
	4607	Panic attacks	Panic attacks	102	114
	4781	Subject discontinued due to weight loss	Weight loss	85	203
	5192	Patient died secondary to complications related to boating accident	Death due to boating accident	173	168

Table 8.1.6.2.1 Normal and potentially clinically significant ranges for clinical chemistry

Parameter	Gender	Age	Normal Range	Expanded Normal Range
Sodium	Female/ Male	18- 59 y		
	Female/ Male	59- 150 y		
Potassium	Female/ Male	18- 150 y		
	Female/ Male	18- 150 y		
Bicarbonate	Female/ Male	18- 150 y		
	Female/ Male	18- 150 y		
Total bilirubin	Female/ Male	18- 150 y		
	Female	18- 59 y		
Alkaline Phosphatase		59- 150 y		
	Male	18- 20 y		
ALT (SGPT)		20- 59 y		
		59- 150 y		
	Female	18- 69 y		
		69- 150y		
AST (SGOT)	Male	18- 69 y		
		69- 150 y		
	Female	18- 150 y		
	Male	18- 150 y		
Creatinine	Female	18- 150 y		
	Male	18- 150 y		
Glucose	Female/ Male	18- 59 y		
		59- 150 y		
Albumin	Female/ Male	18- 69 y		
		69- 150 y		

**Table 8.1.6.2.2 Normal and potentially clinically significant ranges for hemtology**

Parameter	Gender	Age	Normal Range	Expanded Normal Range
Hemoglobin	Female	18- 59 y		
		59- 150 y		
	Male	18- 59 y		
		59- 150 y		
MCV	Female	18- 59 y		
		59- 150 y		
	Male	18- 59 y		
		59- 150 y		
Total WBC	Female/ Male	18- 150 y		
Neutrophils	Female/ Male	18- 150 y		
Lymphocytes	Female/ Male	18- 150 y		
Monocytes	Female/ Male	18- 150 y		
Eosinophils	Female/ Male	18- 150 y		
Basophils	Female/ Male	18- 150 y		
Quantitative platelet count	Female/ Male	18- 60 y		
		60- 150 y		

**Table 8.1.6.2.4 Patient 4015 Hepatic Enzymes Over Time**

Study Visit	Date	ALT (SGPT) U/ L <i>Clinically significant expanded normal range = 0 – 102U/ L</i>	AST (SGOT) U/ L <i>Clinically significant expanded normal range = 0 – 102U/ L</i>
Screen	3/ 24/ 98	42	38
	<b>Open- Label Phase medication began 3/ 29/ 98</b>		
Repeat	4/ 18/ 98	38	41
Day 56	5/ 22/ 98	151	82
Repeat	5/ 29/ 98	87	55
	<b>Last dose of trial medication 6/ 5/ 98</b>		
N/ A	7/ 28/ 98	29	28

**Table 8.1.7.2.1 Criteria for Potentially Significant Changes in Vital Signs**

- Systolic blood pressure greater than or equal to 180mmHg and at least a 20mmHg increase,
- Systolic blood pressure less than or equal to 90mmHg and at least a 20mmHg decrease,
- Diastolic blood pressure greater than or equal to 105mmHg and at least a 15mmHg increase,
- Diastolic blood pressure less than or equal to 50mmHg and at least a 15mmHg decrease,
- Pulse greater than or equal to 120 beats per minutes and at least a 15 beat per minute increase,
- Pulse less than or equal to 50 beats per minutes and at least a 15 beat per minute decrease,
- Weight change of at least 10 pounds.

In addition, subjects with normal blood pressure readings (systolic <120mmHg, diastolic <90mmHg) at Baseline who had treatment-emergent outlier (systolic  $\geq$ 180mmHg, diastolic  $\geq$ 120mmHg) readings were listed, as were those subjects with above-normal baseline readings who had treatment-emergent outlier readings.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**20-358/S-019**

**STATISTICAL REVIEW(S)**

02/15/01

### Statistical Review and Evaluation

<b>NDA#</b>	20-358/SEI-019
<b>Submission Date</b>	May 31, 2000
<b>Due Date</b>	April 1, 2001
<b>Sponsor</b>	Glaxo Wellcome
<b>Name of Drug</b>	Wellbutrin SR (bupropion HCl)
<b>Indication</b>	Treatment of depression
<b>Documents Reviewed</b>	The findings from the statistical analyses.

### Introduction

Results of one multicenter, parallel, randomized, fixed dose, double-blind, placebo-controlled clinical study (Study AK1A4004) consisted of two treatment groups (Placebo and Wellbutrin SR) were submitted to demonstrate the efficacy of Wellbutrin SR compared to placebo for the prevention of relapse/recurrence of depression in subjects previously shown to respond to Wellbutrin SR. The study was conducted in 22 U.S. study centers.

The study consisted of three phases: Screen Phase (1 week duration), Open-label Phase (8 weeks duration), and Double-Blind Phase (44 weeks duration). After giving informed consent, completing screening assessments and meeting inclusion/exclusion criteria, all subjects entered a 1-week Screen Phase. Following completion of the Screen Phase, those subjects who satisfied the inclusion/exclusion criteria were enrolled in the open-Label Phase. Clinic visits were conducted weekly during the 8-week Open-Label Phase. Subjects whose depression responded to treatment during the Open-Label Phase (defined as a CGI-I rating of 1 or 2 at each of the last 3 visits, namely Weeks 6, 7, and 8) were randomized to either Wellbutrin SR or placebo in the Double-Blind Phase. Clinic visits were conducted at Weeks 9, 10, 12, 14, 16 and every 4 weeks thereafter through Week 52. A total of 423 patients were randomized (at Double –Blind Phase) to the treatment groups Wellbutrin SR 150mg (n=210) and PLACEBO (n=213).

The study participants (be  $\geq 18$  years of age) must have met inclusion/exclusion requirements including: (a) had a diagnosis of Recurrent Major Depression as defined in Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV), (b) was currently experiencing a Recurrent Major Depressive Episode, (c) had experienced at least one other depressive episode within the past 60 months and had at least 6 months of euthymia between the current depressive episode and the most recent prior depressive episode, (d) had a minimum score of 18 on the 21-item Hamilton Rating Scale for Depression (HAMD) on Day -6 and Day 0, (e) did not have a history of treatment with

bupropion within the past year, or did not previously participate in a trial in which the subject received bupropion.

The primary objective in the double-blind was to evaluate the efficacy of Wellbutrin SR compared to placebo for the prevention of relapse/recurrence of depression in subjects previously shown to respond to Wellbutrin SR as measured by time to relapse of depression. The secondary objectives of this study were (a) to assess safety over time for subjects who received Wellbutrin SR versus placebo, (b) to assess quality of life, productivity, and resource use over time for subjects who received Wellbutrin SR versus placebo.

The primary efficacy measure of the study was the time (in days) to relapse/recurrence of depression as measured by the time from randomization into the Double-Blind Phase to the first prescription of pharmacotherapy or ECT determined by the investigator to be necessary for the treatment of a relapse/recurrence of depression. The secondary efficacy endpoints were HAMD21, HAMD Depressed Mood Item (item 1), HAMA, CGI-severity, CGI-Improvement, and Quality of Life in Depression Scale (QLDS).

Survival analysis methods were used to compare the two treatment groups with regard to time to relapse/recurrence of depression as defined by the primary endpoint. The primary analysis used the Wilcoxon test to compare the survival curves for the two treatment groups based on Kaplan-Meier analysis of time-to-relapse. The primary analysis was performed on an intent-to-treat population. The intent-to-treat population consisted of all subjects who consumed at least one tablet of double-blind study medication and provided at least one assessment during the Double-Blind Phase of the trial. Times for the censored observations were calculated based on the time from randomization into the Double-Blind Phase to the time of study discontinuation. All statements of statistical significance were based on a two-tailed test with  $\alpha=0.05$  unless stated otherwise. No interim analyses were performed at Double-Blind Phase.

The primary analysis was also performed with observations being censored at the time of the last dose of double-blind medication as opposed to the time of study discontinuation.

The secondary measures were examined between treatment groups via ANCOVA at all time points in the Double-Blind Phase using both observed and LOCF scores for both absolute and change from baseline.

The primary efficacy variable, time-to-relapse, was also analyzed for each gender using Kaplan-Meier analysis of time-to-relapse. Due to small numbers of subjects over 60 years of age and non-Caucasian subjects, no subgroup analyses were done for different age and race groups.

### **Sponsor's Results:**

The results reported here are based on the 423 eligible patients who were subsequently randomized at the double-blind treatment phase. There were 65.01% females among the 423 patients. Majority (87%) of the patients were Caucasians. The mean age of the patients was 39.65 (range from 18-74 years) years. No statistically significant differences among the two treatment groups were observed with respect to age, gender and race. At the time of randomization, the psychiatric history profile of subjects enrolled in the two groups was similar.

A total of 6 (3 from each group) randomized subjects were excluded from the efficacy population because they did not have an efficacy assessment conducted in the Double-Blind Phase. Thus, a total of 417 subjects were included in the efficacy analysis.

Table 1: Number of censored and uncensored Patients over time

Time interval (in days)	Wellbutrin SR (N=207)		Placebo (N=210)	
	Number relapsed	Number Censored	Number relapsed	Number Censored
0-11	2	0	7	0
12-22	13	1	11	3
23-36	16	2	24	7
37-50	9	3	14	5
51-71	13	7	17	5
72-99	5	9	13	5
100-127	6	8	8	6
128-155	4	8	3	6
156-183	0	4	1	7
184-211	1	4	0	2
212-239	0	5	0	2
240-267	1	2	1	2
268-295	1	2	0	1
296 +	0	81	1	59
Total	71 (34.30%)	136 (65.70%)	100 (47.62%)	110 (52.38%)

Table 1 lists the number of censored and uncensored patients over the double blind study period. The placebo-treated patients had higher percentages of relapse (47.62%) and censor (52.38%), as compared to the corresponding percentages (34.30%, 65.70%) for the Wellbutrin SR-treated patients.

The Kaplan-Meier analysis of time-to-relapse resulted a statistically significant difference in favor of Wellbutrin SR when the survival curves for the two treatment groups were compared using both the Wilcoxon ( $p=0.0041$ ) and log-rank ( $p=0.0028$ ) tests. Figure 1 lists the Kaplan-Meier curves of the two treatment groups. Based on the Kaplan-Meier survival estimates and standard errors, a trend ( $p=0.054$ ) toward statistical significance in favor of Wellbutrin SR was seen after 8 weeks of treatment with double-blind medication. Beginning at the next study visit (i.e., Double-Blind Week 12), a statistically significant difference ( $p<0.05$ ) in favor of Wellbutrin SR was seen at each visit week until the end of the study. Survival estimates indicated that more than half (52%) of placebo-treated patients would have become depressed by the end of the study compared to approximately one-third (37%) of Wellbutrin SR-treated patients. At double-Blind period, median times to relapse for the placebo group was 24 weeks;

median time to relapse for Wellbutrin SR was greater than 44 weeks (as this threshold was never met during the study period).

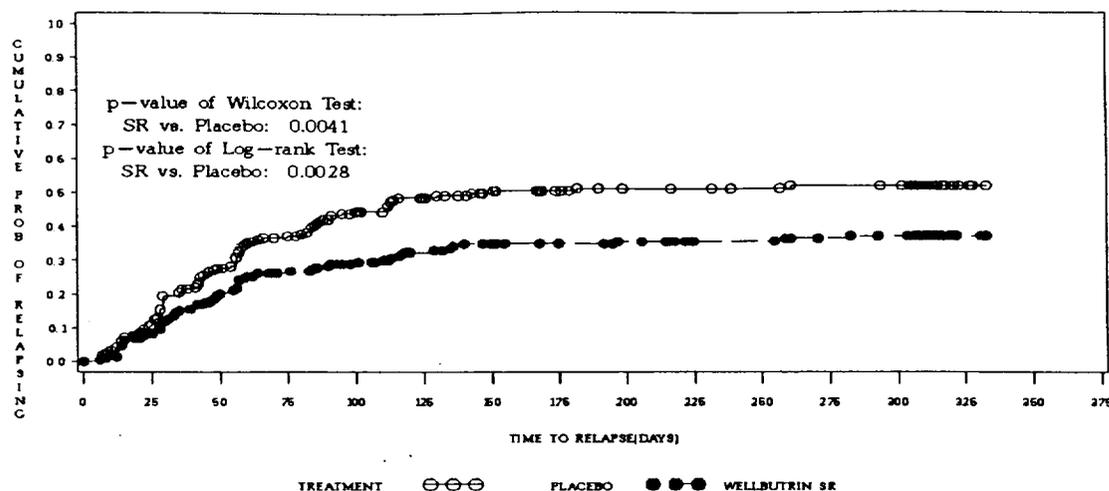


FIGURE 1 KAPLAN-MEIER CURVES OF TIME TO RELAPSE IN DOUBLE-BLIND PHASE

Results were essentially equivalent between the survival analyses (i.e., according to protocol specifications) and supportive survival analyses (i.e., times for the censored observations were calculated based on the time from randomization into the Double-Blind Phase to time of the last dose of double-blind medication).

The efficacy analyses based on each of the secondary efficacy measures demonstrated that at the endpoint LOCF analyses, Wellbutrin SR was not statistically significantly different from Placebo in the double-blind phase (although at some isolated time points, the differences were significant for HAMD item 1, CGI-I).

Subgroups analyses stratifying by gender indicated that effectiveness was similar for male and female subjects. Results of survival analyses for male subjects were  $p=0.043$  and  $p=0.054$  on Wilcoxon and log-rank test, respectively; for female subjects, results on the Wilcoxon and log-rank tests were  $p=0.037$  and  $p=0.020$ , respectively.

#### Adverse Events:

Of the 423 subjects who entered the double-blind phase, 320 (76%) (150 from Wellbutrin SR and 170 from Placebo) did not complete the study. Table 2 lists the reasons for premature discontinuation. The most common reason was for relapse/recurrence of depression, categorized as condition deteriorated. Almost half (47%) of subjects in the placebo group were discontinued for condition deteriorated, while approximately one-third (34%) of subjects in the Wellbutrin SR group were discontinued for the same reason. A total of 10 subjects (8 from Wellbutrin SR and 2 from Placebo) were discontinued from the Double-Blind Phase of the study because of an adverse event. One death (from Wellbutrin SR Group) occurred during double-blind phase of the study. The

patient died from injuries suffered in a boating accident. The investigator indicated that the injuries and death did not have a reasonable possibility of being caused by the study drug.

Table 2: Reasons for Premature Discontinuation from Double-Blind Phase by Treatment Group

Reason for Discontinuation	Placebo (N=213)	Wellbutrin SR (N=210)	Total (N=423)
Adverse Event	2 (<1%)	8 (4%)	10 (2%)
Consent Withdrawn	31 (15%)	36 (17%)	67 (16%)
Lost to Follow Up	21 (10%)	16 (8%)	37 (9%)
Protocol Violation	15 (7%)	19 (9%)	34 (8%)
Condition Deteriorated	100 (47%)	71 (34%)	171 (40%)
Other	1 (<1%)	-	1 (<1%)
<b>Total</b>	<b>170 (80%)</b>	<b>150 (71%)</b>	<b>320 (76%)</b>

### Sponsor's Final Conclusion:

The results of this study demonstrate that treatment with Wellbutrin SR for up to one year is effective for preventing relapse/recurrence of depression. Survival estimates indicated that 63% of the Wellbutrin SR-treated subjects would have been euthymic at the end of the study compared to 48% of placebo-treated subjects ( $p=0.0039$ ). The median time to relapse was 24 weeks for the placebo group, and greater than 44 weeks for the Wellbutrin SR group. The results of this study indicate that treatment is safe and well tolerated for up to one year.

### Reviewer's Analysis and comments:

This reviewer reanalyzed the data set according to the statistical plan specified in the protocol. The findings were consistent with the sponsor's reported findings and was true for both primary and secondary outcome measures. The reviewer was also able to reproduce the figure 1, and this is exactly same as the figure provided by the sponsor.

This reviewer also did Kaplan-Meier analysis considering all of the censored patients as relapsed patients. The time-to-relapse for these patients were considered as their time to censored. The Kaplan-Meier analysis of time-to-relapse resulted a statistically significant difference in favor of Wellbutrin SR when the survival curves for the two treatment groups were compared using both the Wilcoxon ( $p=0.002$ ) and log-rank ( $p=0.018$ ) tests.

This reviewer also compared the two treatment groups with respect to the time-to-censor of the censored patients. The Kaplan-Meier analysis of the censored patients indicated that there was no statistically difference ( $p$ -value: 0.246 from Log-rank test) between the two treatment groups with respect to their time-to-censor.

### Reviewer's Overall Conclusion:

The sponsor designed a trial and analyzed the dataset appropriately to assess the long-term efficacy of the Wellbutrin SR for long-term treatment of depression. The findings demonstrate that Wellbutrin Sr was effective in preventing the relapse/recurrence of depression for up to one year of treatment. This reviewer found sufficient evidence from the statistical analyses of this clinical trial dataset to support the claim of this efficacy supplement application for up to one year.

Ohidul Siddiqui, Ph.D  
Mathematical Statistician

Concur:       Dr. Kun Jin  
  
                  Dr. George Chi

CC:  
Arch NDA # 20-358  
HFD-120/Dr. Katz  
HFD-120/Dr. Laughren  
HFD-120/Dr. Andreason  
HFD-120/Mr. David  
HFD-344/Dr. Barton  
HFD-710/Dr. Chi  
HFD-710/Dr. Jin  
HFD-710/Dr. Siddiqui  
HFD-700/Dr. Anello  
HFD-710/Chron

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***  
**20-358/S-019**

**ADMINISTRATIVE DOCUMENTS**

Trade Name Wellbutrin SR Sustained Release Tablets

Generic Name bupropion HCl

Applicant Name Glaxo Wellcome HFD-120

Approval Date 6-11-01

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /    / NO / X /

b) Is it an effectiveness supplement? YES / X / NO /    /

If yes, what type(SE1, SE2, etc.)? SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO /    /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Maintenance of an antidepressant effect up to 1 year of dosing

d) Did the applicant request exclusivity?

YES / X / NO /    /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_X\_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_X\_/

If yes, NDA # \_\_\_\_\_ Drug Name \_\_\_\_\_

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_X\_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

**1. Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular

form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-358

NDA #

NDA #

2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / \_\_\_ / NO / \_\_\_ /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

NDA # \_\_\_\_\_

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations

(other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was -"yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / \_\_\_ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / \_\_\_ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_X/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # AK1A-4004

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a

previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- (a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /__/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

NDA # \_\_\_\_\_ Study # \_\_\_\_\_

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1\_, Study # **AK1A-4004**

Investigation #\_\_, Study # \_\_\_\_\_

Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND #            YES /X/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
!  
!  
!  
!

Investigation #2 !  
!  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain: \_\_\_\_\_  
!  
!  
!  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the

applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1  
YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2  
YES /\_\_\_/ Explain \_\_\_\_\_ NO /\_\_\_/ Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/ NO /\_X\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title: Regulatory Project Manager

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Office of Division Director  
Title: Division Director

\_\_\_\_\_  
Date

cc:

NDA 20-358

**WELLBUTRIN SR® (bupropion hydrochloride) Tablets**

**Request for Marketing Exclusivity**

Pursuant to Sections 505(c)(3)(D)(iv) and 505(j)(5)(D)(iv) of the Federal Food, Drug, and Cosmetic Act and 21CFR 314.108(b)(5), Glaxo Wellcome Inc. requests three years of exclusivity from the date of approval of Wellbutrin SR® Tablets 100mg and 150mg for prevention of relapse/recurrence of depression.

We hereby certify as to the following:

Item 8, Section 3.3 of this application contains a list of published studies or publicly available reports of clinical investigations known to Glaxo Wellcome through a literature search that are relevant to the use of Wellbutrin for prevention of relapse/recurrence in patients with depression. Glaxo Wellcome has thoroughly searched the literature and to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of Wellbutrin for such use.

Thus, Glaxo Wellcome Inc. is entitled to exclusivity as this application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and sponsored by Glaxo Wellcome Inc. The following investigations are "essential to the approval of the application" in that there are no other data available that could support FDA approval of the application:

**Study AK1A4004**    A Multicenter Placebo-Controlled Study of WELLBUTRIN (bupropion hydrochloride) Sustained Release (SR) for the Prevention of Relapse/Recurrence in Subjects Whose Depression Responded to Treatment with WELLBUTRIN SR

The clinical investigation is defined as "new" as it has not been relied on by the FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by FDA to demonstrate the effectiveness or safety in a new patient population of a previously approved drug application.

This investigation was sponsored by Glaxo Wellcome Inc. in that Glaxo Wellcome Inc. was named in the Form FDA 1571 as the sponsor of the investigational new drug application ; under which it was conducted.

**REGULATORY PROJECT MANAGER  
LABELING REVIEW**

Date: June 7, 2001  
NDA: 20-358  
DRUG: Wellbutrin SR (bupropion Hydrochloride) Sustained-Release Tablets  
Supplements: SLR-018 (dated 5-26-00, and amended on 3-1-01); CBE (no Agency action)  
SE8-019 (dated 11-2-98, and amended on 8-10-00; Agency AE letter dated 2-26-01; Sponsor response to AE letter dated 3-28-01)  
SLR-023 (dated 5-31-00, and amended on 8-10-00, and 3-27-01); Prior Approval Supplement (no Agency action)

Notes of Interest:

- Last Approved labeling supplement: SLR-015 (Approval letter dated 4-10-00; Label Code RL-750).
- SLR-018, submitted under CBE, provides for revisions to the **CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION** sections to incorporate the results of a pK study in patients with liver cirrhosis.
- SLR-023 was submitted as a "prior approval" supplement as requested in an Agency letter dated 11-28-00. The Agency letter requested additional information pertaining to a possible bupropion-warfarin interaction, and requested that the sponsor provide draft labeling revisions.
- The Agency issued an AE letter for SE8-019 in a letter dated 2-26-01 which listed specific labeling revisions. The sponsor responded with a complete response to this action letter in correspondence dated 3-27-01. The submission stated an agreement with the Agency's proposed labeling and the sponsor provided 20 copies of FPL. This FPL, Label Code RL-917, incorporated revisions, verbatim, as requested in the Agency's 2-26-01 letter but did not incorporate the revisions to pending supplemental applications S-018 and S-023.

**REVIEW**

**20-358/SE8-019**

Dated: 3-27-01

CBE: No, Prior Approval

Label Code: RL-917

Reviewed by Medical Officer: Yes, Acceptable

The supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Clinical Trials, INDICATIONS AND USAGE, and DOSAGE AND ADMINISTRATION-Maintenance Treatment** sections of labeling to incorporate the results of GSK's depression relapse prevention study.

The revised sections in the labeling are identical to that which were requested in the Agency AE letter dated 2-26-01.

## CONCLUSIONS

1. The FPL submitted for SE8-019 only incorporates the revisions requested in the Agency AE letter dated 2-26-01. Additionally, the base copy of the FPL submitted is derived from the last approved labeling for Wellbutrin SR (SLR-015/Label Code RL-750). The FPL does not include the revisions submitted under CBE supplement SLR-018 nor the prior approval supplement SLR-023.
2. The medical officer concurs with the revisions made in supplement SE8-019.
3. Although SLR-018 and SLR-023 are pending completed reviews by the clinical and OCPB teams, I recommend issuing an approval action for this labeling since the base document does not include changes made in these supplements which have not been acted upon by the Agency, and the sponsor has agreed to the labeling changes in the Agency's 2-26-01 AE action letter.

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Paul David. RPh  
Regulatory Project Manager

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John Purvis  
Supervisory Consumer Safety Officer

## MEMORANDUM

DATE: February 22, 2001

FROM: Director  
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-358/S-019

SUBJECT: Action Memo for NDA 20-358/S-019, for the use of Wellbutrin (bupropion hydrochloride) in the long term treatment of depression

Supplement S-019 to NDA 20-358, for the use of Wellbutrin (bupropion hydrochloride) in the long-term treatment of patients with depression, was submitted by Glaxo Wellcome on 5/31/00. The supplement contained the results of a single trial of typical design that examined the time to relapse/recurrence in patients randomized to drug or placebo after 8 weeks of open-label drug. The supplement has been reviewed by Dr. Paul Andreason of the division (review dated 2/8/01), Dr. Ohidul Siddiqui, statistician (review dated 2/15/01), and Dr. Tom Laughren, Psychiatric Drugs Team Leader (memo dated 2/13/01). The review team recommends that the application be considered Approvable.

I agree. However, I believe several points need clarification.

As all 3 reviewers describe, the primary outcome was the time to relapse/recurrence, defined as that time that the clinician determined that the patient's condition deteriorated to the point that treatment (either pharmacologic or ECT) was necessary. All reviewers quote the relapse/recurrence rates for drug and placebo patients as 34% and 48%, respectively.

However, Dr. Andreason, on page 7 of his review, describes patients who suffered a "relapse of their index episode of depression" (31 drug, 42 placebo) as distinct from the patients who required pharmacologic intervention, which he refers to as having had a recurrence (40 drug, 58 placebo). The total number of patients in both of these categories adds up to the 34% and 48% quoted above that ostensibly met the protocol definition of "relapse/recurrence", which presumably required a decision to treat with drugs or ECT. Therefore, while the protocol defined outcome of "relapse/recurrence" **required** treatment, Dr. Andreason implies that **only a subset of those considered to have met this protocol specified criterion actually received treatment**. Dr. Andreason has clarified this point in an e-mail dated 2/23/01. In fact, all patients classified as having had a relapse/recurrence did receive pharmacologic intervention. Dr. Andreason's comment in his review refers to a nominal distinction made by the sponsor; that is, the sponsor defined a "relapse" as the need for treatment in the first 5 weeks of the double-blind phase of the trial, whereas if it was determined that the patient needed treatment after the first 5 weeks of the randomized

treatment period, that patient was classified as having had a "recurrence". The distinction is immaterial for our purposes, given that patients in either category met the protocol-specified criteria for "relapse/recurrence".

A significant number of patients did not either complete the trial or suffer a relapse/recurrence; that is, 38% of drug and 33% of placebo patients were classified as censored. Because the primary analysis depends upon the censoring being random, any potential bias introduced by non-random censoring was evaluated by Dr. Siddiqui by considering all censored patients as having met the "relapse/recurrence" criteria. In this analysis, the difference between drug and placebo was still statistically significant.

Finally, Dr. Siddiqui states that the results of the protocol-specified survival analysis were essentially equivalent to the results of the "supportive survival analysis". The former defined the time to censoring as the time from randomization to study discontinuation, while the latter apparently considered the time to censoring as the time from randomization to the time of the last dose of double-blind medication. According to Dr. Siddiqui, there were a number of patients who continued in the trial despite the fact that they had stopped taking medication some time before they were censored (or before they completed).

I agree with the review team that the application is Approvable, and I will issue the attached Approvable letter with appended draft labeling.

Russell Katz, M.D.

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** February 13, 2001

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approvable Action for Wellbutrin SR (bupropion)  
for the longer-term treatment of depression

**TO:** File NDA 20-358/S-019  
[Note: This overview should be filed with the 5-31-00  
original submission of this supplement.]

**1.0 BACKGROUND**

Bupropion is a reuptake inhibitor for norepinephrine, serotonin, and dopamine that was approved for the treatment of depression in December, 1985 (Wellbutrin; NDA 18-644). A sustained release form of bupropion, Wellbutrin SR, was approved for depression 10-4-96. This supplement provides data in support of longer-term antidepressant efficacy for Wellbutrin SR.

We did not meet with the sponsor to discuss the development program for this claim, nor did we have a pre-supplement meeting. The study supporting this supplement (AK1A4004) was conducted under IND

Since the proposal is to use the currently approved Wellbutrin SR formulations for this expanded claim, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. The primary review of the clinical efficacy and safety data was done by Paul Andreason, M.D. from the clinical group. Ohidul Siddiqui, Ph.D., from the Division of Biometrics, reviewed the efficacy data for study AK1A4004, the single long-term trial for which results were submitted in support of this supplement.

The original supplement for this expanded indication (S-019) was submitted 5-31-00. There was no safety~update.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee.

## **2.0 CHEMISTRY**

As Wellbutrin SR is a marketed product, there were no chemistry issues requiring review for this supplement.

## **3.0 PHARMACOLOGY**

As Wellbutrin SR is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

## **4.0 BIOPHARMACEUTICS**

As Wellbutrin SR is a marketed product, there were no biopharmaceutics issues requiring review for this supplement.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Summary of Study AK1A4004**

Study AK1A4004 was a randomized, double-blind, parallel group, multicenter study of the discontinuation/time to relapse design. There were 22 US sites. The study enrolled adult outpatients meeting DSM-IV criteria for major depression, recurrent type. Patients were treated on an open basis with Wellbutrin SR for 8 weeks (150 mg bid, i.e., total daily dose of 300 mg). Patients who responded during this open treatment period were randomized (1:1) to continuation of their same Wellbutrin SR dose or placebo. "Response" was defined as a CGI Improvement score of 1 (very much improved) or 2 (much improved) for the last 3 weeks (6, 7, and 8). Patients were then observed for a period of up to 44 weeks. The primary outcome for this study was specified in the protocol as time to "relapse" of a depressive episode, defined as follows: prescription of pharmacotherapy or ECT, as judged to be necessary by the investigator for the treatment of depression. The primary efficacy analysis was based on the Wilcoxon test of Kaplan-Meier survival curves.

Of 828 patients who began the open label phase, 518 completed to 56 days, and of these, 423 were randomized into the double-blind phase (n=210 for Wellbutrin SR and n=213 for placebo). However, of these, 417 (n=207 for Wellbutrin SR and n=210 for placebo) contributed data for the ITT analysis (all

randomized subjects who received at least one dose of drug and had efficacy assessments at baseline and at least one followup time). Patients were roughly 2/3 female, predominantly Caucasian, and the mean age was about 39 years. Time to relapse was significantly longer for Wellbutrin SR treated patients than for placebo treated patients (for Wilcoxon,  $p = 0.0041$ ). Crude relapse rates, based on 44 weeks, were 100/210 (48%) for placebo and 71/207 (34%) for Wellbutrin SR. Most of the relapses occurred early, primarily in the 1-3 month interval.

-Results were similar across gender.

-No data were provided in this supplement pertinent to the question of dose/response for maintaining an antidepressant response during longer-term maintenance treatment.

-It is difficult to clinically interpret the effect sizes on the primary measure observed, i.e., rate of relapse for this study in terms of differences between drug and placebo. However, the difference observed was comparable to what has been observed for other drugs approved for the longer-term treatment of depression.

Comment: Both Drs. Andreason and Siddiqui concluded that study AK1A4004 provides evidence of longer-term maintenance of antidepressant efficacy (up to 44 weeks) in patients who had improved and remained improved during an 8 week open Wellbutrin SR treatment phase, and I agree.

## 5.2 Safety Data

Dr. Andreason has reviewed the relatively small amount of additional safety data for Wellbutrin SR in study AK1A4004 in detail. Essentially there were no surprises and no new findings that would change our impressions about the short-term or long-term safety of this drug, or that would impact on labeling.

## 5.3 Clinical Sections of Labeling

As noted, we have modified the sponsor's proposed additions to labeling regarding these new efficacy findings, i.e., changes under Clinical Pharmacology (Clinical Trials), Indications and Usage, and Dosage and Administration (Maintenance).

## 6.0 WORLD LITERATURE

There were no literature reports included in this supplement.

## 7.0 FOREIGN REGULATORY ACTIONS

I am not aware of any language regarding study AK1A4004 having been added to any foreign.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

We decided not to take this supplement to the PDAC.

## **9.0 DSI INSPECTIONS**

To my knowledge, no inspections were done for this supplement.

## **10.0 APPROVABLE LETTER**

An approvable letter acknowledging our decision to proceed with an approval action pending agreement on labeling has been included with the approvable package.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Glaxo Wellcome has submitted sufficient data to support the conclusion that Wellbutrin SR is effective in the longer-term treatment of depression. I recommend that we issue the attached approvable letter with our proposed labeling for this product.

cc:  
Orig NDA 20-358/S-019  
HFD-120/Division File  
HFD-120/TLaughren/RKatz/PAndreason/PDavid