CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

Trade Name: Wellbutrin and Wellbutrin SR

Generic Name: bupropion hydrochloride

Sponsor: GlaxoSmithKline

Approval Date: December 23, 2013

Indication: Treatment of major depressive disorder (MDD)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 18644/S-046, S-047
NDA 20358/S-053, S-054

SUPPLEMENT APPROVAL

GlaxoSmithKline
Attention: Jaisri Giridhar, PhD, DABT, RAC
Manager, Neurosciences
Global Regulatory Affairs
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398

Dear Dr. Giridhar:

Please refer to the following Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 18644 Wellbutrin (bupropion hydrochloride) 75 mg and 100 mg Tablets and NDA 20358 Wellbutrin SR (bupropion hydrochloride) Sustained-Release 100 mg, 150 mg, and 200 mg Tablets:

- Prior Approval Labeling Supplements NDA 18644/S-046 and 20358/S-053, dated and received November 30, 2012, provide for labeling revisions to the **Pregnancy** section of labeling. The June 21, 2013 submission constituted a complete response to our May 28, 2013 complete response letter. We acknowledge receipt of your amendments dated December 20, 2013.

- Prior Approval Labeling Supplements NDA 18644/S-047 and 20358/S-054, dated December 11, 2012 and received December 12, 2012, proposing a draft label to be in compliance with the Physician Labeling Rule.

  We acknowledge receipt of your amendments dated:

March 13, 2013	April 19, 2013	December 4, 2013
April 1, 2013	June 21, 2013	December 20, 2013
April 4, 2013	September 13, 2013	
April 9, 2013	October 24, 2013	

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your December 20, 2013, submissions include final printed labeling (FPL) for your package inserts and Medication Guides. We have not reviewed the FPL. You are responsible

for assuring that the wording in the printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling (Full Prescribing Information and Medication Guide)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
12/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 018644/S-046
NDA 020358/S-053

COMPLETE RESPONSE

GlaxoSmithKline LLC
Attention: Mary E. Martinson
Vice President, Neurosciences
Global Regulatory Affairs
5 Crescent Drive
Philadelphia, PA 11912

Dear Ms. Martinson:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NDA 018644 S-046 WELLBUTRIN (bupropion hydrochloride) 75 mg and 100 mg tablets, and NDA 020358 S-053 WELLBUTRIN SR (bupropion hydrochloride) sustained-release 100 mg, 150 mg, and 200 mg tablets.

We acknowledge receipt of your amendments dated December 20, 2012, April 1, 2013, April 9, 2013, and April 30, 2013.

These "Prior Approval" labeling supplemental new drug applications propose draft labeling revisions to the (b) (4) updating the information about use during pregnancy (b) (4)
We have completed the review of your applications and have determined that we cannot approve these applications in their present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

We reviewed the studies you referenced in your cover letter that look at pregnancy outcomes following maternal exposure to bupropion in the first trimester that reported a potential increased risk of some congenital cardiovascular malformations. Some data suggests potential increased risk of ventricular septal defects or increased risk of left outflow tract heart defects; however, the findings are not consistent across studies. In addition, there are limitations to the studies which make it difficult to interpret the findings and reach conclusions about causality.

We briefly summarize our findings from each of the referenced studies:

- On January 27, 2006, you submitted a pharmacoepidemiologic cohort study conducted using the Ingenix database to evaluate the association between maternal first trimester bupropion

exposure and risk of congenital and cardiac anomalies. In a later publication by Cole et al. in 2007, the authors concluded that the study did not support bupropion exposure in the first trimester of pregnancy as a risk factor for infant cardiac malformations. This study also had the following limitations:

- There were a limited number of cases with cardiovascular malformations (overall and specific malformations) that were exposed to bupropion in the first trimester.
- The study likely lacked power to detect differences in cardiac outcomes between infants exposed to bupropion vs. other antidepressants in utero.

- On July 1, 2010, Alwan et al. published a case control study that suggested an increased risk of congenital left ventricular outflow tract obstruction (LVOTO) among infants born to mothers exposed to bupropion in the first trimester of pregnancy. Alwan et al. concluded that mothers exposed to bupropion during the first trimester were at a higher risk of giving birth to infants with LVOTO; however, the study results might have been subject to the effect of recall bias and confounding by indication.

- On March 3, 2011, you voluntarily submitted a reanalysis of the 2006 data refining exposures and outcomes to match the definitions employed in the study by Alwan et al. The crude odds ratio (OR) for LVOTO comparing mothers exposed to bupropion monotherapy during the first trimester to mothers exposed to other antidepressant monotherapy during the first trimester, based on 5 cases between the two exposures was 4.00 (95% CI 0.33-34.93), which is a confidence interval upper bound indicating that a 34-fold increased risk might be statistically plausible. However, the reanalysis has the following limitations:
  - The low number of cases precluded any adjustment for potential confounders.
  - Since LVOTO is a subset of cardiac malformations, the study likely had even less power than the original analyses.
  - The study report noted a 0.68 (95% CI 0.24-1.92) unadjusted OR of any congenital cardiac malformation comparing the same exposure groups. The point estimate was less than one, but the in-aggregate congenital cardiac malformation unadjusted OR was 1.74 (95% CI 0.59-5.09), a CI indicating a five-fold risk might be statistically plausible.

- On August 10, 2012, a study report you submitted from the Slone Epidemiology Center at Boston University suggested that taking bupropion during the first trimester of pregnancy can result in an increased risk for ventricular septal defects (VSD) in the newborn. However, this study holds the following limitations:
  - The limited number of exposed cases prevented adjustment for more than one or two covariates.
  - Use of patient interview to obtain drug exposure after conception may lead mothers having a child with a birth defect to recall drug exposure to a better extent than mothers having children without birth defects (recall bias).
  - It is possible that the small number of exposed cases leads to unstable point estimates and these results are chance findings. The null finding for use of bupropion in combination with other antidepressants has no plausible explanation.

- A prior study by Alwan et al found a signal only with bupropion and left-sided cardiac defects, while the current study found only a signal between bupropion and VSD. There is no explanation for these differences.

Overall, we find that the studies are inconclusive and inconsistent and that the potential limitations of these studies prevent one from determining a causal association. (b) (4)

(b) (4)

Current evidence suggests that the use of bupropion during pregnancy is reasonably safe. Furthermore, there are risks associated with untreated depression, both for the mother and the infant, which may outweigh any potential risk for birth defects. (b) (4)

LABELING

Please submit draft labeling revised as follows in Physician's Labeling Rule "PLR" format.

HIGHLIGHTS

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

(b) (4)

TABLE OF CONTENTS

- (b) (4)

FULL PRESCRIBING INFORMATION

8 Use in Specific Populations
8.1 Pregnancy

Pregnancy Category C

Risk Summary

(b) (4)

(b) (4)

Clinical Considerations

Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

(b) (4)

Human Data

Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

(b) (4)

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

(b) (4)

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

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

If you have any questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
05/28/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WELLBUTRIN safely and effectively. See full prescribing information for WELLBUTRIN.

WELLBUTRIN (bupropion hydrochloride) Tablets, for oral use
Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**
- **Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2.4, 2.5)	03/2013
Contraindications (4)	03/2013

INDICATIONS AND USAGE

WELLBUTRIN is an aminoketone antidepressant, indicated for the treatment of major depressive disorder (MDD). (1)

DOSAGE AND ADMINISTRATION

- Starting Dose: 200 mg per day given as 100 mg twice daily (2.1)
- General: Increase dose gradually to reduce seizure risk. (2 1, 5.3)
- After 3 days, may increase the dose to 300 mg per day, given as 100 mg 3 times daily at an interval of at least 6 hours between doses. (2.1)
- Usual target dose: 300 mg per day as 100 mg 3 times daily. (2.1)
- Maximum dose: 450 mg per day given as 150 mg 3 times daily. (2.1)
- Periodically reassess the dose and need for maintenance treatment. (2.1)
- Moderate to severe hepatic impairment: 75 mg once daily. (2.2, 8.7)
- Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.2, 8.7)
- Renal Impairment: Consider reducing the dose and/or frequency. (2.3, 8.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg and 100 mg. (3)

CONTRAINDICATIONS

- Seizure disorder. (4, 5.3)
- Current or prior diagnosis of bulimia or anorexia nervosa. (4, 5.3)
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3)
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with WELLBUTRIN or within 14 days of stopping treatment with WELLBUTRIN. Do not use WELLBUTRIN within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start WELLBUTRIN in a patient who is being treated with linezolid or intravenous methylene blue. (4, 7.6)
- Known hypersensitivity to bupropion or other ingredients of WELLBUTRIN. (4, 5.7)

WARNINGS AND PRECAUTIONS

- Seizure risk: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 450 mg. Discontinue if seizure occurs. (4, 5.3, 7.3)
- Hypertension: WELLBUTRIN can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment. (5.4)
- Activation of mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms. (5.5)
- Psychosis and other neuropsychiatric reactions: Instruct patients to contact a healthcare professional if such reactions occur. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and ≥1% more than placebo rate) are: agitation, dry mouth, constipation, headache/migraine, nausea/vomiting, dizziness, excessive sweating, tremor, insomnia, blurred vision, tachycardia, confusion, rash, hostility, cardiac arrhythmias, and auditory disturbance. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2B6 inducers: Dose increase may be necessary if coadministered with CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) based on clinical response, but should not exceed the maximum recommended dose. (7.1)
- Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide). Consider dose reduction when using with bupropion. (7.2)
- Drugs that lower seizure threshold: Dose WELLBUTRIN with caution. (5.3, 7.3)
- Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with WELLBUTRIN. (7.4)
- MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with WELLBUTRIN. (7.6)
- Drug-laboratory test interactions: WELLBUTRIN can cause false-positive urine test results for amphetamines. (7.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: Month Year

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation *[see Warnings and Precautions (5.2)]*. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although WELLBUTRIN® is not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

WELLBUTRIN (bupropion hydrochloride) is indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM**)**.

The efficacy of WELLBUTRIN in the treatment of a major depressive episode was established in two 4-week controlled inpatient trials and one 6-week controlled outpatient trial of adult subjects with MDD *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions for Use

To minimize the risk of seizure, increase the dose gradually *[see Warnings and Precautions (5.3)]*. Increases in dose should not exceed 100 mg per day in a 3-day period. WELLBUTRIN Tablets should be swallowed whole and not crushed, divided, or chewed. WELLBUTRIN may be taken with or without food.

The recommended starting dose is 200 mg per day, given as 100 mg twice daily. After 3 days of dosing, the dose may be increased to 300 mg per day, given as 100 mg 3 times daily, with at least 6 hours between successive doses. Dosing above 300 mg per day may be accomplished using the 75- or 100-mg tablets.

A maximum of 450 mg per day, given in divided doses of not more than 150 mg each, may be considered for patients who show no clinical improvement after several weeks of treatment at 300 mg per day. Administer the 100-mg tablet 4 times daily to not exceed the limit of 150 mg in a single dose.

It is generally agreed that acute episodes of depression require several months or longer of antidepressant drug treatment beyond the response in the acute episode. It is unknown whether the dose of WELLBUTRIN needed for maintenance treatment is identical to the dose that provided an initial response. Periodically reassess the need for maintenance treatment and the appropriate dose for such treatment.

2.2 Dose Adjustment in Patients With Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to15), the maximum dose of WELLBUTRIN is 75 mg per day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Dose Adjustment in Patients With Renal Impairment

Consider reducing the dose and/or frequency of WELLBUTRIN in patients with renal impairment (Glomerular Filtration Rate <90 mL/min) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with WELLBUTRIN. Conversely, at least 14 days should be allowed after stopping WELLBUTRIN before starting an MAOI antidepressant *[see Contraindications (4) and Drug Interactions (7.6)]*.

2.5 Use of WELLBUTRIN With Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start WELLBUTRIN in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions. In a patient who requires more urgent treatment of a psychiatric

condition, non-pharmacological interventions, including hospitalization, should be considered *[see Contraindications (4) and Drug Interactions (7.6)]*.

In some cases, a patient already receiving therapy with WELLBUTRIN may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of hypertensive reactions in a particular patient, WELLBUTRIN should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with WELLBUTRIN may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with WELLBUTRIN is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use *[see Contraindications (4) and Drug Interactions (7.6)]*.

3 DOSAGE FORMS AND STRENGTHS

- 75 mg – yellow-gold, round, biconvex tablets printed with “WELLBUTRIN 75”.
- 100 mg – red, round, biconvex tablets printed with “WELLBUTRIN 100”.

4 CONTRAINDICATIONS

- WELLBUTRIN is contraindicated in patients with a seizure disorder.
- WELLBUTRIN is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with WELLBUTRIN *[see Warnings and Precautions (5.3)]*.
- WELLBUTRIN is contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*.
- The use of MAOIs (intended to treat psychiatric disorders) concomitantly with WELLBUTRIN or within 14 days of discontinuing treatment with WELLBUTRIN is contraindicated. There is an increased risk of hypertensive reactions when WELLBUTRIN is used concomitantly with MAOIs. The use of WELLBUTRIN within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting WELLBUTRIN in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.4), and Drug Interactions (7.6)]*.
- WELLBUTRIN is contraindicated in patients with known hypersensitivity to bupropion or other ingredients of WELLBUTRIN. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger subjects for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 subjects treated) are provided in Table 1.

Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Subjects Treated
Increases Compared With Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared With Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases *[see Boxed Warning]*.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for WELLBUTRIN should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

WELLBUTRIN is not approved for smoking cessation treatment; however, bupropion HCl sustained-release is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide *[see Boxed Warning and Adverse Reactions (6.2)]*. Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

In many of these cases, a causal relationship to bupropion treatment is not certain, because depressed mood can be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke.

5.3 Seizure

WELLBUTRIN can cause seizure. The risk of seizure is dose-related. The dose should not exceed 450 mg per day. Increase the dose gradually. Discontinue WELLBUTRIN and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with WELLBUTRIN. WELLBUTRIN is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs *[see Contraindications (4) and Drug Interactions (7.3)]*. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Incidence of Seizure With Bupropion Use: Bupropion is associated with seizures in approximately 0.4% (4/1,000) of patients treated at doses up to 450 mg per day. The estimated seizure incidence for WELLBUTRIN increases almost 10-fold between 450 and 600 mg per day.

The risk of seizure can be reduced if the dose of WELLBUTRIN does not exceed 450 mg per day, given as 150 mg 3 times daily, and the titration rate is gradual.

5.4 Hypertension

Treatment with WELLBUTRIN can result in elevated blood pressure and hypertension. Assess blood pressure before initiating treatment with WELLBUTRIN, and monitor periodically during treatment. The risk of hypertension is increased if WELLBUTRIN is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity *[see Contraindications (4)]*.

Data from a comparative trial of the sustained-release formulation of bupropion HCl, nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of

sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with sustained-release bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive heart failure (N = 36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled trials assessing the safety of bupropion in patients with a recent history of myocardial infarction or unstable cardiac disease.

5.5 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating WELLBUTRIN, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). WELLBUTRIN is not approved for use in treating bipolar depression.

5.6 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with WELLBUTRIN have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Instruct patients to contact a healthcare professional if such reactions occur.

5.7 Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring medical treatment. In addition, there have been rare, spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue WELLBUTRIN and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

There are reports of arthralgia, myalgia, fever with rash and other serum sickness-like symptoms suggestive of delayed hypersensitivity.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Suicidal thoughts and behaviors in adolescents and young adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Neuropsychiatric symptoms and suicide risk in smoking cessation treatment *[see Boxed Warning and Warnings and Precautions (5.2)]*

- Seizure *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Activation of mania or hypomania *[see Warnings and Precautions (5.5)]*
- Psychosis and other neuropsychiatric reactions *[see Warnings and Precautions (5.6)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions Leading to Discontinuation of Treatment: Adverse reactions were sufficiently troublesome to cause discontinuation of treatment with WELLBUTRIN in approximately 10% of the 2,400 subjects and healthy volunteers who participated in clinical trials during the product's initial development. The more common events causing discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note, however, that many of these events occurred at doses that exceed the recommended daily dose.

Commonly Observed Adverse Reactions: Adverse reactions commonly encountered in subjects treated with WELLBUTRIN are agitation, dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, tremor, dizziness, excessive sweating, blurred vision, tachycardia, confusion, rash, hostility, cardiac arrhythmia, and auditory disturbance.

Table 2 summarizes the adverse reactions that occurred in placebo-controlled trials at an incidence of at least 1% of subjects receiving WELLBUTRIN and more frequently in these subjects than in the placebo group.

Table 2. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency Than Placebo in Controlled Clinical Trials

Adverse Reaction	WELLBUTRIN (n = 323) %	Placebo (n = 185) %
Cardiovascular		
Cardiac arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6

Dermatologic		
Pruritus	2.2	0.0
Rash	8.0	6.5
Gastrointestinal		
Appetite increase	3.7	2.2
Constipation	26.0	17.3
Dyspepsia	3.1	2.2
Nausea/vomiting	22.9	18.9
Genitourinary		
Impotence	3.4	3.1
Menstrual complaints	4.7	1.1
Urinary frequency	2.5	2.2
Musculoskeletal		
Arthritis	3.1	2.7
Neurological		
Akathisia	1.5	1.1
Cutaneous temperature disturbance	1.9	1.6
Dry mouth	27.6	18.4
Excessive sweating	22.3	14.6
Headache/migraine	25.7	22.2
Impaired sleep quality	4.0	1.6
Insomnia	18.6	15.7
Sedation	19.8	19.5
Sensory disturbance	4.0	3.2
Tremor	21.1	7.6
Neuropsychiatric		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased libido	3.1	1.6
Delusions	1.2	1.1
Euphoria	1.2	0.5
Hostility	5.6	3.8
Nonspecific		
Fever/chills	1.2	0.5
Special Senses		

Auditory disturbance	5.3	3.2
Blurred vision	14.6	10.3
Gustatory disturbance	3.1	1.1

Other Adverse Reactions Observed During the Clinical Development of WELLBUTRIN: The conditions and duration of exposure to WELLBUTRIN varied greatly, and a substantial proportion of the experience was gained in open and uncontrolled clinical settings. During this experience, numerous adverse events were reported; however, without appropriate controls, it is impossible to determine with certainty which events were or were not caused by WELLBUTRIN. The following enumeration is organized by organ system and describes events in terms of their relative frequency of reporting in the database.

The following definitions of frequency are used: Frequent adverse reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions are those occurring in 1/100 to 1/1,000 subjects, while rare events are those occurring in less than 1/1,000 subjects.

Cardiovascular: Frequent was edema; infrequent were chest pain, electrocardiogram (ECG) abnormalities (premature beats and nonspecific ST-T changes), and shortness of breath/dyspnea; rare were flushing, and myocardial infarction.

Dermatologic: Infrequent was alopecia.

Endocrine: Infrequent was gynecomastia; rare was glycosuria.

Gastrointestinal: Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice; rare was intestinal perforation.

Genitourinary: Frequent was nocturia; infrequent were vaginal irritation, testicular swelling, urinary tract infection, painful erection, and retarded ejaculation; rare were enuresis, and urinary incontinence.

Neurological: Frequent were ataxia/incoordination, seizure, myoclonus, dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were electroencephalogram (EEG) abnormality, and impaired attention.

Neuropsychiatric: Frequent were mania/hypomania, increased libido, hallucinations, decrease in sexual function, and depression; infrequent were memory impairment, depersonalization, psychosis, dysphoria, mood instability, paranoia, formal thought disorder, and frigidity; rare was suicidal ideation.

Oral Complaints: Frequent was stomatitis; infrequent were toothache, bruxism, gum irritation, and oral edema.

Respiratory: Infrequent were bronchitis and shortness of breath/dyspnea; rare was pulmonary embolism.

Special Senses: Infrequent was visual disturbance; rare was diplopia.

Nonspecific: Frequent were flu-like symptoms; infrequent was nonspecific pain; rare was overdose.

Altered Appetite and Weight: A weight loss of greater than 5 lbs occurred in 28% of subjects receiving WELLBUTRIN. This incidence is approximately double that seen in

comparable subjects treated with tricyclics or placebo. Furthermore, while 35% of subjects receiving tricyclic antidepressants gained weight, only 9.4% of subjects treated with WELLBUTRIN did. Consequently, if weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight reducing potential of WELLBUTRIN should be considered.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of WELLBUTRIN and are not described elsewhere in the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body (General): Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.

Cardiovascular: Hypertension (in some cases severe), orthostatic hypotension, third degree heart block.

Endocrine: Syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia, hypoglycemia.

Gastrointestinal: Esophagitis, hepatitis.

Hemic and Lymphatic: Ecchymosis, leukocytosis, leukopenia, thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Musculoskeletal: Muscle rigidity/fever/rhabdomyolysis, muscle weakness.

Nervous System: Aggression, coma, completed suicide, delirium, dream abnormalities, paranoid ideation, paresthesia, restlessness, suicide attempt, unmasking of tardive dyskinesia.

Skin and Appendages: Stevens-Johnson syndrome, angioedema, exfoliative dermatitis, urticaria.

Special Senses: Tinnitus, increased intraocular pressure.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect WELLBUTRIN

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between WELLBUTRIN and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6: *Ticlopidine and Clopidogrel:* Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of WELLBUTRIN may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP2B6: *Ritonavir, Lopinavir, and Efavirenz:* Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of WELLBUTRIN may be necessary when coadministered with ritonavir, lopinavir, or efavirenz *[see Clinical Pharmacology (12.3)]* but should not exceed the maximum recommended dose.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure *[see Clinical Pharmacology (12.3)]*. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded.

7.2 Potential for WELLBUTRIN to Affect Other Drugs

Drugs Metabolized by CYP2D6: Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, coadministration of WELLBUTRIN with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with WELLBUTRIN, it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with WELLBUTRIN and such drugs may require increased doses of the drug *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs That Lower Seizure Threshold

Use extreme caution when coadministering WELLBUTRIN with other drugs that lower seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

7.4 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering WELLBUTRIN concomitantly with these drugs.

7.5 Use With Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with WELLBUTRIN. The consumption of alcohol during treatment with WELLBUTRIN should be minimized or avoided.

7.6 MAO Inhibitors

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days

should elapse between discontinuation of an MAOI intended to treat depression and initiation of treatment with WELLBUTRIN. Conversely, at least 14 days should be allowed after stopping WELLBUTRIN before starting an MAOI antidepressant *[see Dosage and Administration (2.4, 2.5) and Contraindications (4)]*.

7.7 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses twice the MRHD and greater. WELLBUTRIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Human Data: Data from the international bupropion Pregnancy Registry (675 first-trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data: In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at 50 mg/kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

8.3 Nursing Mothers

Bupropion and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when WELLBUTRIN is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Of the approximately 6,000 subjects who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥65 years and 47 were aged ≥75 years. In addition, several hundred subjects aged ≥65 years participated in clinical trials using the immediate-release formulation of bupropion (depression trials). No

overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function *[see Dosage and Administration (2.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Consider a reduced dose and/or dosing frequency of WELLBUTRIN in patients with renal impairment (Glomerular Filtration Rate: <90 mL/min). Bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of WELLBUTRIN is 75 mg daily. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing *[see Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Bupropion is not a controlled substance.

9.2 Abuse

Humans: Controlled clinical trials conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose trials does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (that could not be tested because of the risk of seizure) might be modestly attractive to those who abuse CNS stimulant drugs.

Animals: Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

10 OVERDOSAGE

10.1 Human Overdose Experience

Overdoses of up to 30 grams or more of bupropion have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

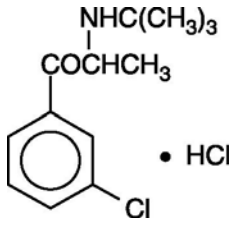
10.2 Overdosage Management

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physician's Desk Reference (PDR). Call 1-800-222-1222 or refer to www.poison.org.

There are no known antidotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

11 DESCRIPTION

WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO•HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



WELLBUTRIN is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; 100-mg tablet – FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of the antidepressant action of bupropion is not known, but is presumed to be related to noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase.

12.3 Pharmacokinetics

Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Absorption: The absolute bioavailability of WELLBUTRIN in humans has not been determined because an intravenous formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

In humans, following oral administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved within 2 hours. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma level is maintained in chronic use.

Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism: Bupropion is extensively metabolized in humans. Three metabolites are active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of

bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high as or higher than those of bupropion.

Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 3 hours after administration of WELLBUTRIN and are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg per day.

Elimination: Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged bupropion.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Renal Impairment: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-trial comparison between normal subjects and subjects with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage renal failure. A second trial, comparing normal subjects and subjects with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that after a single 150-mg dose of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects with impaired renal function, while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is

extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion may be reduced by impaired renal function. WELLBUTRIN should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 groups were minimal.

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild-to-moderate hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in subjects with mild-to-moderate hepatic cirrhosis. In subjects with severe hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table 3).

Table 3. Pharmacokinetics of Bupropion and Metabolites in Patients With Severe Hepatic Cirrhosis: Ratio Relative to Healthy Matched Controls

	C_{max}	**AUC**	**$t_{½}$**	**T_{max}[a]**
Bupropion	1.69	3.12	1.43	0.5 h
Hydroxybupropion	0.31	1.28	3.88	19 h
Threo/erythrohydrobupropion amino alcohol	0.69	2.48	1.96	20 h

[a] = Difference.

Left Ventricular Dysfunction: During a chronic dosing trial with bupropion in 14 depressed subjects with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared with healthy volunteers.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy trials involving subjects dosed in a range of 300 to 750 mg per day, on a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic trial demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger

subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another single- and multiple-dose pharmacokinetics trial suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites *[see Use in Specific Populations (8.5)]*.

Gender: Pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations of bupropion. The mean systemic exposure (AUC) was approximately 13% higher in male volunteers compared with female volunteers. The clinical significance of this finding is unknown.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there were no statistically significant differences in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Drug Interactions: *Potential for Other Drugs to Affect WELLBUTRIN:* In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between WELLBUTRIN and drugs that are inhibitors or inducers of CYP2B6. In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion.

Inhibitors of CYP2B6: Ticlopidine, Clopidogrel: In a trial in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine, respectively. The exposures (C_{max} and AUC) of hydroxybupropion were decreased 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

Prasugrel: Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel increased bupropion C_{max} and AUC values by 14% and 18%, respectively, and decreased C_{max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by 32% and 24%, respectively.

Cimetidine: The threohydrobupropion metabolite of bupropion does not appear to be produced by cytochrome P450 enzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of bupropion 300 mg with and without cimetidine 800 mg, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively of the combined moieties of threohydrobupropion and erythrohydrobupropion.

Citalopram: Citalopram did not affect the pharmacokinetics of bupropion and its three metabolites.

Inducers of CYP2B6: Ritonavir and Lopinavir: In a healthy volunteer trial, ritonavir 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%,

respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

In a second healthy volunteer trial, ritonavir 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer trial, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by 50% and 31%, respectively.

Efavirenz: In a trial in healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the AUC and C_{max} of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, whereas C_{max} of hydroxybupropion was increased by 50%.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion.

Potential for WELLBUTRIN to Affect Other Drugs: Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one trial, following chronic administration of bupropion 100 mg three times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be potential for clinically important alterations of blood levels of co-administered drugs.

Drugs Metabolized by CYP2D6: In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Citalopram: Although citalopram is not primarily metabolized by CYP2D6, in one trial bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively.

Lamotrigine: Multiple oral doses of bupropion had no statistically significant effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the MRHD, respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such

lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

The efficacy of WELLBUTRIN in the treatment of major depressive disorder was established in two 4-week, placebo-controlled trials in adult inpatients with MDD (Trials 1 and 2 in Table 4) and in one 6-week, placebo-controlled trial in adult outpatients with MDD (Trial 3 in Table 4). In the first trial, the dose range of WELLBUTRIN was 300 mg to 600 mg per day administered in 3 divided doses; 78% of subjects were treated with doses of 300 mg to 450 mg per day. The trial demonstrated the efficacy of WELLBUTRIN as measured by the Hamilton Depression Rating Scale (HDRS) total score, the HDRS depressed mood item (item 1), and the Clinical Global Impressions-severity score (CGI-S). The second trial included 2 doses of WELLBUTRIN (300 and 450 mg per day) and placebo. This trial demonstrated the effectiveness of WELLBUTRIN for only the 450-mg-per-day dose. The efficacy results were statistically significant for the HDRS total score and the CGI-S score, but not for HDRS item 1. In the third trial, outpatients were treated with 300 mg per day of WELLBUTRIN. This trial demonstrated the efficacy of WELLBUTRIN as measured by the HDRS total score, the HDRS item 1, the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S score, and the CGI-Improvement Scale (CGI-I) score. Effectiveness of WELLBUTRIN in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials.

Table 4. Efficacy of WELLBUTRIN for the Treatment of Major Depressive Disorder

		Primary Efficacy Measure: HDRS		
Trial Number	**Treatment Group**	**Mean Baseline Score (SD)**	**LS Mean Score at Endpoint Visit (SE)**	**Placebo-substracted Difference[a] (95% CI)**
Trial 1	WELLBUTRIN 300-600 mg/day[b] (n = 48)	28.5 (5.1)	14.9 (1.3)	-4.7 (-8.8, -0.6)
	Placebo (n = 27)	29.3 (7.0)	19.6 (1.6)	--
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**

Trial 2	WELLBUTRIN 300 mg/day (n = 36)	32.4 (5.9)	-15.5 (1.7)	-4.1
	WELLBUTRIN 450 mg/day[b] (n = 34)	34.8 (4.6)	-17.4 (1.7)	-5.9 (-10.5, -1.4)
	Placebo (n=39)	32.9 (5.4)	-11.5 (1.6)	--
Trial 3	WELLBUTRIN 300 mg/day[b] (n = 110)	26.5 (4.3)	-12.0 (NA)	-3.9 (-5.7, -1.0)
	Placebo (n = 106)	27.0 (3.5)	-8.7 (NA)	--

n: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval included for doses that were demonstrated to be effective; NA: not available.

[a] Difference (drug minus placebo) in least-squares estimates with respect to the primary efficacy parameter. For Trial 1, it refers to the mean score at the endpoint visit; for Trials 2 and 3, it refers to the mean change from baseline to the endpoint visit.

[b] Doses that are demonstrated to be statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

WELLBUTRIN Tablets, 75 mg of bupropion hydrochloride, are yellow-gold, round, biconvex tablets printed with “WELLBUTRIN 75” in bottles of 100 (NDC 0173-0177-55).

WELLBUTRIN Tablets, 100 mg of bupropion hydrochloride, are red, round, biconvex tablets printed with “WELLBUTRIN 100” in bottles of 100 (NDC 0173-0178-55).

Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with WELLBUTRIN and counsel them in its appropriate use.

A patient Medication Guide about “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions,” “Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions,” and “What Other Important Information Should I Know About WELLBUTRIN?” is available for WELLBUTRIN. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any

questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Advise patients regarding the following issues and to alert their prescriber if these occur while taking WELLBUTRIN.

Suicidal Thoughts and Behaviors: Instruct patients, their families, and/or their caregivers to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Advise families and caregivers of patients to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or healthcare professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment: Although WELLBUTRIN is not indicated for smoking cessation treatment, it contains the same active ingredient as ZYBAN® which is approved for this use. Advise patients, families and caregivers that quitting smoking, with or without ZYBAN, may trigger nicotine withdrawal symptoms (e.g., including depression or agitation), or worsen pre-existing psychiatric illness. Some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

Severe Allergic Reactions: Educate patients on the symptoms of hypersensitivity and to discontinue WELLBUTRIN if they have a severe allergic reaction.

Seizure: Instruct patients to discontinue and not restart WELLBUTRIN if they experience a seizure while on treatment. Advise patients that the excessive use or abrupt discontinuation of alcohol, benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure. Advise patients to minimize or avoid use of alcohol.

Bupropion-Containing Products: Educate patients that WELLBUTRIN contains the same active ingredient (bupropion hydrochloride) found in ZYBAN, which is used as an aid to smoking cessation treatment, and that WELLBUTRIN should not be used in combination with ZYBAN or any other medications that contain bupropion (such as WELLBUTRIN SR®, the sustained-release formulation and WELLBUTRIN XL® or FORFIVO XL™, the extended-release formulations, and APLENZIN®, the extended-release formulation of bupropion hydrobromide). In addition, there are a number of generic bupropion HCl products for the immediate-, sustained-, and extended-release formulations.

Potential for Cognitive and Motor Impairment: Advise patients that any CNS-active drug like WELLBUTRIN may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Advise patients that until they are reasonably certain that WELLBUTRIN does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. WELLBUTRIN may lead to decreased alcohol tolerance.

Concomitant Medications: Counsel patients to notify their healthcare provider if they are taking or plan to take any prescription or over-the-counter drugs because WELLBUTRIN and other drugs may affect each others' metabolisms.

Pregnancy: Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

Precautions for Nursing Mothers: Advise patients that WELLBUTRIN is present in human milk in small amounts.

Storage Information: Instruct patients to store WELLBUTRIN at room temperature, between 59°F and 86°F (15°C to 30°C) and keep the tablets dry and out of the light.

Administration Information: Instruct patients to take WELLBUTRIN in equally divided doses 3 or 4 times a day, with doses separated by least 6 hours to minimize the risk of seizure. Instruct patients if they miss a dose, not to take an extra tablet to make up for the missed dose and to take the next tablet at the regular time because of the dose-related risk of seizure. Instruct patients that WELLBUTRIN Tablets should be swallowed whole and not crushed, divided, or chewed. WELLBUTRIN can be taken with or without food.

Manufactured for:

GlaxoSmithKline
Research Triangle Park, NC 27709

WLT:XPI

MEDICATION GUIDE
WELLBUTRIN® (WELL byu-trin)
(bupropion hydrochloride) Tablets

Read this Medication Guide carefully before you start taking WELLBUTRIN and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about WELLBUTRIN, ask your healthcare provider or pharmacist.

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to quit smoking; and the third section is entitled "What Other Important Information Should I Know About WELLBUTRIN?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your healthcare provider or your family member's healthcare provider about**:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.

2. Depression or other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines

to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

It is not known if WELLBUTRIN is safe and effective in children under the age of 18.

Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking.

Although WELLBUTRIN is not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN® which is used to help patients quit smoking.

Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking bupropion to help them quit smoking. These symptoms can develop during treatment with bupropion or after stopping treatment with bupropion.

If you, your family member, or your caregiver notice agitation, hostility, depression, or changes in thinking or behavior that are not typical for you, or you have any of the following symptoms, stop taking bupropion and call your healthcare provider right away:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without bupropion, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking bupropion, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without bupropion.

What Other Important Information Should I Know About WELLBUTRIN?

- **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN, especially in people:**
  - with certain medical problems.
  - who take certain medicines.

The chance of having seizures increases with higher doses of WELLBUTRIN. For more information, see the sections “Who should not take WELLBUTRIN?” and “What should I tell my healthcare provider before taking WELLBUTRIN?” Tell your healthcare provider about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are taking WELLBUTRIN unless your healthcare provider has said it is okay to take them.**

If you have a seizure while taking WELLBUTRIN, stop taking the tablets and call your healthcare provider right away. Do not take WELLBUTRIN again if you have a seizure.

- **High blood pressure (hypertension). Some people get high blood pressure that can be severe, while taking WELLBUTRIN.** The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.
- **Manic episodes.** Some people may have periods of mania while taking WELLBUTRIN, including:
  - Greatly increased energy
  - Severe trouble sleeping
  - Racing thoughts
  - Reckless behavior

- Unusually grand ideas
- Excessive happiness or irritability
- Talking more or faster than usual

If you have any of the above symptoms of mania, call your healthcare provider.

- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your healthcare provider.
- **Severe allergic reactions. Some people can have severe allergic reactions to WELLBUTRIN. Stop taking WELLBUTRIN and call your healthcare provider right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

What is WELLBUTRIN?

WELLBUTRIN is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take WELLBUTRIN?

Do not take WELLBUTRIN if you

- have or had a seizure disorder or epilepsy.
- have or had an eating disorder such as anorexia nervosa or bulimia.
- **are taking any other medicines that contain bupropion, including ZYBAN (used to help people stop smoking) APLENZIN®, FORFIVO XL™, WELLBUTRIN SR®, or WELLBUTRIN XL®**. Bupropion is the same active ingredient that is in WELLBUTRIN.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines, and you stop using them all of a sudden.
- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - do not take an MAOI within 2 weeks of stopping WELLBUTRIN unless directed to do so by your healthcare provider.
  - do not start WELLBUTRIN if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your healthcare provider.

- are allergic to the active ingredient in WELLBUTRIN, bupropion, or to any of the inactive ingredients. See the end of this Medication Guide for a complete list of ingredients in WELLBUTRIN.

What should I tell my healthcare provider before taking WELLBUTRIN?
Tell your healthcare provider if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

Tell your healthcare provider about your other medical conditions including if you:
- have liver problems, especially cirrhosis of the liver.
- have kidney problems.
- have, or have had, an eating disorder, such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink alcohol.
- abuse prescription medicines or street drugs.
- are pregnant or plan to become pregnant.
- are breastfeeding. WELLBUTRIN passes into your milk in small amounts.

Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are taking WELLBUTRIN.

How should I take WELLBUTRIN?
- Take WELLBUTRIN exactly as prescribed by your healthcare provider.
- Take WELLBUTRIN at the same time each day.
- Take your doses of WELLBUTRIN at least 6 hours apart.
- **Do not chew, cut, or crush WELLBUTRIN tablets.**
- You may take WELLBUTRIN with or without food.
- If you miss a dose, do not take an extra dose to make up for the dose you missed. Wait and take your next dose at the regular time. **This is very important.** Too much WELLBUTRIN can increase your chance of having a seizure.

- If you take too much WELLBUTRIN, or overdose, call your local emergency room or poison control center right away.
- **Do not take any other medicines while taking WELLBUTRIN unless your healthcare provider has told you it is okay.**
- If you are taking WELLBUTRIN for the treatment of major depressive disorder, it may take several weeks for you to feel that WELLBUTRIN is working. Once you feel better, it is important to keep taking WELLBUTRIN exactly as directed by your healthcare provider. Call your healthcare provider if you do not feel WELLBUTRIN is working for you.
- Do not change your dose or stop taking WELLBUTRIN without talking with your healthcare provider first.

What should I avoid while taking WELLBUTRIN?

- Limit or avoid using alcohol during treatment with WELLBUTRIN. If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your risk of having seizures.
- Do not drive a car or use heavy machinery until you know how WELLBUTRIN affects you. WELLBUTRIN can affect your ability to do these things safely.

What are possible side effects of WELLBUTRIN?

See **"What Other Important Information Should I Know About WELLBUTRIN?"**

WELLBUTRIN can cause serious side effects.

The most common side effects of WELLBUTRIN include:

- Nervousness
- Dry mouth
- Constipation
- Headache
- Nausea or vomiting
- Dizziness
- Heavy sweating
- Shakiness (tremor)
- Trouble sleeping
- Blurred vision
- Fast heartbeat

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

Tell your healthcare provider right away about any side effects that bother you.

These are not all the possible side effects of WELLBUTRIN. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

How should I store WELLBUTRIN?

- Store WELLBUTRIN at room temperature between 59°F and 86°F (15°C to 30°C).
- Keep WELLBUTRIN Tablets dry and out of the light.

Keep WELLBUTRIN and all medicines out of the reach of children.

General Information about WELLBUTRIN.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELLBUTRIN for a condition for which it was not prescribed. Do not give WELLBUTRIN to other people, even if they have the same symptoms you have. It may harm them.

If you take a urine drug screening test, WELLBUTRIN may make the test result positive for amphetamines. If you tell the person giving you the drug screening test that you are taking WELLBUTRIN, they can do a more specific drug screening test that should not have this problem.

This Medication Guide summarizes important information about WELLBUTRIN. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about WELLBUTRIN that is written for healthcare professionals.

For more information about WELLBUTRIN, go to www.wellbutrin.com or call 1-888-825-5249.

What are the ingredients in WELLBUTRIN?

Active ingredient: bupropion hydrochloride.
Inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide; 100-mg tablet – FD&C Red No. 40

Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:

GlaxoSmithKline
Research Triangle Park, NC 27709

Month year
WLT: MG

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WELLBUTRIN SR safely and effectively. See full prescribing information for WELLBUTRIN SR.

WELLBUTRIN SR (bupropion hydrochloride) Sustained-Release Tablets, for oral use
Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants. (5.1)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)**
- **Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.2)**

RECENT MAJOR CHANGES

Dosage and Administration (2.4, 2.5)	03/2013
Contraindications (4)	03/2013

INDICATIONS AND USAGE

- WELLBUTRIN SR is an aminoketone antidepressant, indicated for the treatment of major depressive disorder (MDD). (1)

DOSAGE AND ADMINISTRATION

- Starting Dose: 150 mg per day (2.1)
- General: Increase dose gradually to reduce seizure risk. (2 1, 5.3)
- After 3 days, may increase the dose to 300 mg per day, given as 150 mg twice daily at an interval of at least 8 hours. (2.1)
- Usual target dose: 300 mg per day as 150 mg twice daily. (2.1)
- Maximum dose: 400 mg per day, given as 200 mg twice daily, for patients not responding to 300 mg per day. (2.1)
- Periodically reassess the dose and need for maintenance treatment. (2.1)
- Moderate to severe hepatic impairment: 100 mg daily or 150 mg every other day. (2.2, 8.7)
- Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.2, 8.7)
- Renal Impairment: Consider reducing the dose and/or frequency. (2.3, 8.6)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg, 150 mg, 200 mg. (3)

CONTRAINDICATIONS

- Seizure disorder. (4, 5.3)
- Current or prior diagnosis of bulimia or anorexia nervosa. (4, 5.3)
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3)
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with WELLBUTRIN SR or within 14 days of stopping treatment with WELLBUTRIN SR. Do not use WELLBUTRIN SR within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start WELLBUTRIN SR in a patient who is being treated with linezolid or intravenous methylene blue. (4, 7.6)
- Known hypersensitivity to bupropion or other ingredients of WELLBUTRIN SR. (4, 5.7)

WARNINGS AND PRECAUTIONS

- Seizure risk: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 400 mg. Discontinue if seizure occurs. (4, 5.3, 7.3)
- Hypertension: WELLBUTRIN SR can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment. (5.4)
- Activation of mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms. (5.5)
- Psychosis and other neuropsychiatric reactions: Instruct patients to contact a healthcare professional if such reactions occur. (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and ≥2% more than placebo rate) are: headache, dry mouth, nausea, insomnia, dizziness, pharyngitis, constipation, agitation, anxiety, abdominal pain, tinnitus, tremor, palpitation, myalgia, sweating, rash, and anorexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2B6 inducers: Dose increase may be necessary if coadministered with CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) based on clinical response, but should not exceed the maximum recommended dose. (7.1)
- Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide). Consider dose reduction when using with bupropion. (7.2)
- Drugs that lower seizure threshold: Dose WELLBUTRIN SR with caution. (5.3, 7.3)
- Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with WELLBUTRIN SR. (7.4)
- MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with WELLBUTRIN SR. (7.6)
- Drug-laboratory test interactions: WELLBUTRIN SR can cause false-positive urine test results for amphetamines. (7.7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: Month Year

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation *[see Warnings and Precautions (5.2)]*. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although WELLBUTRIN® SR is not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur *[*see *Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

WELLBUTRIN SR (bupropion hydrochloride) is indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM**)**.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled inpatient trials and one 6-week controlled outpatient trial of adult subjects with MDD *[see Clinical Studies (14)]*.

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 Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions for Use

To minimize the risk of seizure, increase the dose gradually *[see Warnings and Precautions (5.3)]*. WELLBUTRIN SR Tablets should be swallowed whole and not crushed, divided, or chewed. WELLBUTRIN SR may be taken with or without food.

The usual adult target dose for WELLBUTRIN SR is 300 mg per day, given as 150 mg twice daily. Initiate dosing with 150 mg per day given as a single daily dose in the morning. After 3 days of dosing, the dose may be increased to the 300-mg-per-day target dose, given as 150 mg twice daily. There should be an interval of at least 8 hours between successive doses. A maximum of 400 mg per day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg per day. To avoid high peak concentrations of bupropion and/or its metabolites, do not exceed 200 mg in any single dose.

It is generally agreed that acute episodes of depression require several months or longer of antidepressant drug treatment beyond the response in the acute episode. It is unknown whether the dose of WELLBUTRIN SR needed for maintenance treatment is identical to the dose that provided an initial response. Periodically reassess the need for maintenance treatment and the appropriate dose for such treatment.

2.2 Dose Adjustment in Patients With Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of WELLBUTRIN SR is 100 mg per day or 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

2.3 Dose Adjustment in Patients With Renal Impairment

Consider reducing the dose and/or frequency of WELLBUTRIN SR in patients with renal impairment (Glomerular Filtration Rate <90 mL/min) *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

2.4 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with WELLBUTRIN SR. Conversely, at least 14 days should be allowed after stopping WELLBUTRIN SR before starting an MAOI antidepressant *[see Contraindications (4) and Drug Interactions (7.6)]*.

2.5 Use of WELLBUTRIN SR With Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start WELLBUTRIN SR in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions. In a patient who requires more urgent treatment of a psychiatric condition, non-pharmacological interventions, including hospitalization, should be considered *[see Contraindications (4) and Drug Interactions (7.6)]*.

In some cases, a patient already receiving therapy with WELLBUTRIN SR may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of hypertensive reactions in a particular patient, WELLBUTRIN SR should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with WELLBUTRIN SR may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with WELLBUTRIN SR is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use *[see Contraindications (4) and Drug Interactions (7.6)]*.

3 DOSAGE FORMS AND STRENGTHS

- 100 mg – blue, round, biconvex, film-coated, sustained-release tablets printed with "WELLBUTRIN SR 100".
- 150 mg – purple, round, biconvex, film-coated, sustained-release tablets printed with "WELLBUTRIN SR 150".
- 200 mg – light pink, round, biconvex, film-coated, sustained-release tablets printed with "WELLBUTRIN SR 200".

4 CONTRAINDICATIONS

- WELLBUTRIN SR is contraindicated in patients with a seizure disorder.
- WELLBUTRIN SR is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate-release formulation of bupropion *[see Warnings and Precautions (5.3)]*.
- WELLBUTRIN SR is contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs *[see Warnings and Precautions (5.3) and Drug Interactions (7.3)]*.
- The use of MAOIs (intended to treat psychiatric disorders) concomitantly with WELLBUTRIN SR or within 14 days of discontinuing treatment with WELLBUTRIN SR is contraindicated. There is an increased risk of hypertensive reactions when WELLBUTRIN SR is used concomitantly with MAOIs. The use of WELLBUTRIN SR within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting WELLBUTRIN SR in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated *[see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.4), and Drug Interactions (7.6)]*.
- WELLBUTRIN SR is contraindicated in patients with known hypersensitivity to bupropion or other ingredients of WELLBUTRIN SR. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported *[see Warnings and Precautions (5.7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger subjects for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 subjects treated) are provided in Table 1.

Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Subjects Treated
Increases Compared With Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared With Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases *[see Boxed Warning]*.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for WELLBUTRIN SR should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

WELLBUTRIN SR is not approved for smoking cessation treatment; however, ZYBAN® is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide *[see Boxed Warning and Adverse Reactions (6.2)]*. Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

In many of these cases, a causal relationship to bupropion treatment is not certain, because depressed mood can be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke.

5.3 Seizure

WELLBUTRIN SR can cause seizure. The risk of seizure is dose-related. The dose should not exceed 400 mg per day. Increase the dose gradually. Discontinue WELLBUTRIN SR and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with WELLBUTRIN SR. WELLBUTRIN SR is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs *[*see *Contraindications (4) and Drug Interactions (7.3)]*. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Incidence of Seizure With Bupropion Use: When WELLBUTRIN SR is dosed up to 300 mg per day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg per day.

The risk of seizure can be reduced if the dose of WELLBUTRIN SR does not exceed 400 mg per day, given as 200 mg twice daily, and the titration rate is gradual.

5.4 Hypertension

Treatment with WELLBUTRIN SR can result in elevated blood pressure and hypertension. Assess blood pressure before initiating treatment with WELLBUTRIN SR, and monitor periodically during treatment. The risk of hypertension is increased if WELLBUTRIN SR is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity *[see Contraindications (4)]*.

Data from a comparative trial of the sustained-release formulation of bupropion HCl, nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of

sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with sustained-release bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive heart failure (N = 36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled trials assessing the safety of bupropion in patients with a recent history of myocardial infarction or unstable cardiac disease.

5.5 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating WELLBUTRIN SR, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). WELLBUTRIN SR is not approved for use in treating bipolar depression.

5.6 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with WELLBUTRIN SR have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Instruct patients to contact a healthcare professional if such reactions occur.

5.7 Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring medical treatment. In addition, there have been rare, spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue WELLBUTRIN SR and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

There are reports of arthralgia, myalgia, fever with rash and other serum sickness-like symptoms suggestive of delayed hypersensitivity.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Suicidal thoughts and behaviors in adolescents and young adults *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Neuropsychiatric symptoms and suicide risk in smoking cessation treatment *[see Boxed Warning and Warnings and Precautions (5.2)]*

- Seizure *[see Warnings and Precautions (5.3)]*
- Hypertension *[see Warnings and Precautions (5.4)]*
- Activation of mania or hypomania *[see Warnings and Precautions (5.5)]*
- Psychosis and other neuropsychiatric reactions *[see Warnings and Precautions (5.6)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions Leading to Discontinuation of Treatment: In placebo-controlled clinical trials, 4%, 9%, and 11% of the placebo, 300-mg-per-day, and 400-mg-per-day groups, respectively, discontinued treatment due to adverse reactions. The specific adverse reactions leading to discontinuation in at least 1% of the 300-mg-per-day or 400-mg-per-day groups and at a rate at least twice the placebo rate are listed in Table 2.

Table 2. Treatment Discontinuations Due to Adverse Reactions in Placebo-Controlled Trials

Adverse Reaction	Placebo (n = 385)	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)
Rash	0.0%	2.4%	0.9%
Nausea	0.3%	0.8%	1.8%
Agitation	0.3%	0.3%	1.8%
Migraine	0.3%	0.0%	1.8%

Commonly Observed Adverse Reactions: Adverse reactions from Table 3 occurring in at least 5% of subjects treated with WELLBUTRIN SR and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg-per-day dose groups.

WELLBUTRIN SR 300 mg per day: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

WELLBUTRIN SR 400 mg per day: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Adverse reactions reported in placebo-controlled trials are presented in Table 3. Reported adverse reactions were classified using a COSTART-based Dictionary.

Table 3. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency Than Placebo in Controlled Clinical Trials

Body System/ Adverse Reaction	WELLBUTRIN SR 300 mg/day	WELLBUTRIN SR 400 mg/day	Placebo (n = 385)

	(n = 376)	(n = 114)	
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%

Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage[a]	0%	2%	—
Urinary tract infection	1%	0%	—

[a] Incidence based on the number of female subjects.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of subjects.

Other Adverse Reactions Observed During the Clinical Development of Bupropion: In addition to the adverse reactions noted above, the following adverse reactions have been reported in clinical trials with the sustained-release formulation of bupropion in depressed subjects and in nondepressed smokers, as well as in clinical trials with the immediate-release formulation of bupropion.

Adverse reaction frequencies represent the proportion of subjects who experienced a treatment-emergent adverse reaction on at least one occasion in placebo-controlled trials for depression (n = 987) or smoking cessation (n = 1,013), or subjects who experienced an adverse reaction requiring discontinuation of treatment in an open-label surveillance trial with WELLBUTRIN SR (n = 3,100). All treatment-emergent adverse reactions are included except those listed in Table 3, those listed in other safety-related sections of the prescribing information, those subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those not reasonably associated with the use of the drug, and those that were not serious and occurred in fewer than 2 subjects.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions

are those occurring in 1/100 to 1/1,000 subjects, while rare events are those occurring in less than 1/1,000 subjects.

Body (General): Infrequent were chills, facial edema, and photosensitivity. Rare was malaise.

Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare were syncope and myocardial infarction.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue.

Hemic and Lymphatic: Infrequent was ecchymosis.

Metabolic and Nutritional: Infrequent were edema and peripheral edema.

Musculoskeletal: Infrequent were leg cramps.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania.

Respiratory: Rare was bronchospasm.

Special Senses: Infrequent were accommodation abnormality and dry eye.

Urogenital: Infrequent were impotence, polyuria, and prostate disorder.

Changes in Body Weight: In placebo-controlled trials, subjects experienced weight gain or weight loss as shown in Table 4.

Table 4. Incidence of Weight Gain and Weight Loss (≥5 lbs.) in Placebo-Controlled Trials

Weight Change	WELLBUTRIN SR 300 mg/day (n = 339)	WELLBUTRIN SR 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In clinical trials conducted with the immediate-release formulation of bupropion, 35% of subjects receiving tricyclic antidepressants gained weight, compared with 9% of subjects treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN SR should be considered.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of WELLBUTRIN SR and are not described elsewhere in the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body (General): Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness *[see Warnings and Precautions (5.7)]*.

Cardiovascular: Complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe), phlebitis, and pulmonary embolism.

Digestive: Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, pancreatitis, and stomach ulcer.

Endocrine: Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic: Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional: Glycosuria.

Musculoskeletal: Muscle rigidity/fever/rhabdomyolysis and muscle weakness.

Nervous System: Abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory: Pneumonia.

Skin: Alopecia, angioedema, exfoliative dermatitis, hirsutism, and Stevens-Johnson syndrome.

Special Senses: Deafness, increased intraocular pressure, and mydriasis.

Urogenital: Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect WELLBUTRIN SR

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between WELLBUTRIN SR and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6: *Ticlopidine and Clopidogrel:* Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of WELLBUTRIN SR may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP2B6: *Ritonavir, Lopinavir, and Efavirenz:* Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of WELLBUTRIN SR may be necessary when coadministered with ritonavir, lopinavir, or efavirenz *[see Clinical Pharmacology (12.3)]* but should not exceed the maximum recommended dose.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure *[see Clinical Pharmacology (12.3)]*. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded.

7.2 Potential for WELLBUTRIN SR to Affect Other Drugs

Drugs Metabolized by CYP2D6: Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, coadministration of WELLBUTRIN SR with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with WELLBUTRIN SR, it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with WELLBUTRIN SR and such drugs may require increased doses of the drug *[see Clinical Pharmacology (12.3)]*.

7.3 Drugs That Lower Seizure Threshold

Use extreme caution when coadministering WELLBUTRIN SR with other drugs that lower seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually *[see Contraindications (4) and Warnings and Precautions (5.3)]*.

7.4 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering WELLBUTRIN SR concomitantly with these drugs.

7.5 Use With Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with WELLBUTRIN SR. The consumption of alcohol during treatment with WELLBUTRIN SR should be minimized or avoided.

7.6 MAO Inhibitors

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days

should elapse between discontinuation of an MAOI intended to treat depression and initiation of treatment with WELLBUTRIN SR. Conversely, at least 14 days should be allowed after stopping WELLBUTRIN SR before starting an MAOI antidepressant *[see Dosage and Administration (2.4, 2.5) and Contraindications (4)]*.

7.7 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to the maximum recommended human dose (MRHD) and greater and decreased fetal weights were seen at doses twice the MRHD and greater. WELLBUTRIN SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Human Data: Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data: In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at 50 mg/kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

8.3 Nursing Mothers

Bupropion and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise caution when WELLBUTRIN SR is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Of the approximately 6,000 subjects who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥65 years and 47 were aged ≥75 years. In addition, several hundred subjects aged ≥65 years participated in clinical trials using the immediate-release formulation of bupropion (depression trials). No

overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function *[see Dosage and Administration (2.3), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Consider a reduced dose and/or dosing frequency of WELLBUTRIN SR in patients with renal impairment (Glomerular Filtration Rate: <90 mL/min). Bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of WELLBUTRIN SR is 100 mg per day or 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing *[*see *Dosage and Administration (2.2)* and *Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Bupropion is not a controlled substance.

9.2 Abuse

Humans: Controlled clinical trials of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose trials does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (that could not be tested because of the risk of seizure) might be modestly attractive to those who abuse CNS stimulant drugs.

Animals: Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

10 OVERDOSAGE

10.1 Human Overdose Experience

Overdoses of up to 30 grams or more of bupropion have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

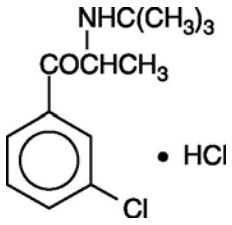
10.2 Overdosage Management

Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physician's Desk Reference (PDR). Call 1-800-222-1222 or refer to www.poison.org.

There are no known antidotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

11 DESCRIPTION

WELLBUTRIN SR (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO•HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



WELLBUTRIN SR is supplied for oral administration as 100-mg (blue), 150-mg (purple), and 200-mg (light pink), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of the antidepressant action of bupropion is not known, but is presumed to be related to noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase.

12.3 Pharmacokinetics

Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of the individual enantiomers have not been studied. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

Absorption: The absolute bioavailability of WELLBUTRIN SR in humans has not been determined because an intravenous formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

In humans, following oral administration of WELLBUTRIN SR, peak plasma concentration (C_{max}) of bupropion is usually achieved within 3 hours.

In a trial comparing chronic dosing with WELLBUTRIN SR 150 mg twice daily to bupropion immediate-release formulation 100 mg 3 times daily, the steady state C_{max} for bupropion after WELLBUTRIN SR administration was approximately 85% of those achieved after bupropion immediate-release formulation administration. Exposure (AUC) to bupropion was equivalent for both formulations. Bioequivalence was also demonstrated for all three major active metabolites (i.e., hydroxybupropion, threohydrobupropion and erythrohydrobupropion) for both C_{max} and AUC. Thus, at steady state, WELLBUTRIN SR given twice daily, and the

immediate-release formulation of bupropion given 3 times daily, are essentially bioequivalent for both bupropion and the 3 quantitatively important metabolites.

WELLBUTRIN SR can be taken with or without food. Bupropion C_{max} and AUC wasincreased by 11% to 35% and 16% to 19%, respectively, when WELLBUTRIN SR was administered with food to healthy volunteers in three trials. The food effect is not considered clinically significant.

Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas, the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism: Bupropion is extensively metabolized in humans. Three metabolites are active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high as or higher than those of bupropion.

Following a single dose administration of WELLBUTRIN SR in humans, C_{max} of hydroxybupropion occurs approximately 6 hours post-dose and is approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (±5) hours and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33(±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to 450 mg per day.

Elimination: Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose was excreted as unchanged bupropion.

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced

renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Renal Impairment: There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-trial comparison between normal subjects and subjects with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage renal failure. A second trial, comparing normal subjects and subjects with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min), showed that after a single 150-mg dose of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects with impaired renal function, while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion may be reduced by impaired renal function. WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered *[see Use in Specific Populations (8.6)]*.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 groups were minimal.

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild–to-moderate hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in subjects with mild–to-moderate hepatic cirrhosis. In subjects with severe hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table 5).

Table 5. Pharmacokinetics of Bupropion and Metabolites in Patients With Severe Hepatic Cirrhosis: Ratio Relative to Healthy Matched Controls

	C_{max}	**AUC**	**$t_{½}$**	**T_{max}[a]**
Bupropion	1.69	3.12	1.43	0.5 h
Hydroxybupropion	0.31	1.28	3.88	19 h
Threo/erythrohydrobupropion amino alcohol	0.69	2.48	1.96	20 h

[a] = Difference.

Left Ventricular Dysfunction: During a chronic dosing trial with bupropion in 14 depressed subjects with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared with healthy volunteers.

Age: The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy trials involving subjects dosed in a range of 300 to 750 mg per day, on a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic trial demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another single- and multiple-dose pharmacokinetics trial suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites *[see Use in Specific Populations (8.5)]*.

Gender: Pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations of bupropion. The mean systemic exposure (AUC) was approximately 13% higher in male volunteers compared with female volunteers. The clinical significance of this finding is unknown.

Smokers: The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there were no statistically significant differences in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Drug Interactions: *Potential for Other Drugs to Affect WELLBUTRIN SR:* In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between WELLBUTRIN SR and drugs that are inhibitors or inducers of CYP2B6. In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion.

Inhibitors of CYP2B6: Ticlopidine, Clopidogrel: In a trial in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine, respectively. The exposures (C_{max} and AUC) of hydroxybupropion were decreased 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

Prasugrel: Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel increased bupropion C_{max} and AUC values by 14% and 18%, respectively, and

decreased C_{max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by 32% and 24%, respectively.

Cimetidine: The threohydrobupropion metabolite of bupropion does not appear to be produced by cytochrome P450 enzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of bupropion 300 mg with and without cimetidine 800 mg, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively of the combined moieties of threohydrobupropion and erythrohydrobupropion.

Citalopram: Citalopram did not affect the pharmacokinetics of bupropion and its three metabolites.

Inducers of CYP2B6: Ritonavir and Lopinavir: In a healthy volunteer trial, ritonavir 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

In a second healthy volunteer trial, ritonavir 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer trial, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by 50% and 31%, respectively.

Efavirenz: In a trial in healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the AUC and C_{max} of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, whereas C_{max} of hydroxybupropion was increased by 50%.

Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion.

Potential for WELLBUTRIN SR to Affect Other Drugs: Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one trial, following chronic administration of bupropion 100 mg three times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be potential for clinically important alterations of blood levels of co-administered drugs.

Drugs Metabolized by CYP2D6: In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion.

Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Citalopram: Although citalopram is not primarily metabolized by CYP2D6, in one trial bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively.

Lamotrigine: Multiple oral doses of bupropion had no statistically significant effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the MRHD, respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

The efficacy of the immediate-release formulation of bupropion in the treatment of major depressive disorder was established in two 4-week, placebo-controlled trials in adult inpatients with MDD (Trials 1 and 2 in Table 6) and in one 6-week, placebo-controlled trial in adult outpatients with MDD (Trial 3 in Table 6). In the first trial, the dose range of bupropion was 300 mg to 600 mg per day administered in divided doses; 78% of subjects were treated with doses of 300 mg to 450 mg per day. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion by the Hamilton Depression Rating Scale (HDRS) total score, the HDRS depressed mood item (item 1), and the Clinical Global Impressions severity score (CGI-S). The second trial included 2 doses of the immediate-release formulation of bupropion (300 and 450 mg per day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450-mg-per-day dose. The efficacy results were significant for the HDRS total score and the CGI-S score, but not for HDRS item 1. In the third trial, outpatients were treated with 300 mg per day of the immediate-release formulation of bupropion. This trial demonstrated the efficacy of the immediate-release formulation of bupropion as measured by the HDRS total score, the HDRS item 1, the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S score, and the CGI-Improvement Scale (CGI-I) score.

Table 6. Efficacy of Immediate-Release Bupropion for the Treatment of Major Depressive Disorder

Trial Number	Treatment Group	Primary Efficacy Measure: HDRS		
		Mean Baseline Score (SD)	**LS Mean Score at Endpoint Visit (SE)**	**Placebo-substracted Difference[a] (95% CI)**
Trial 1	Immediate-Release Bupropion 300-600 mg/day[b] (n = 48)	28.5 (5.1)	14.9 (1.3)	-4.7 (-8.8, -0.6)
	Placebo (n = 27)	29.3 (7.0)	19.6 (1.6)	--
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Trial 2	Immediate-Release Bupropion 300 mg/day (n = 36)	32.4 (5.9)	-15.5 (1.7)	-4.1
	Immediate-Release Bupropion 450 mg/day[b] (n = 34)	34.8 (4.6)	-17.4 (1.7)	-5.9 (-10.5, -1.4)
	Placebo (n = 39)	32.9 (5.4)	-11.5 (1.6)	--
Trial 3	Immediate-Release Bupropion 300 mg/day[b] (n = 110)	26.5 (4.3)	-12.0 (NA)	-3.9 (-5.7, -1.0)
	Placebo (n = 106)	27.0 (3.5)	-8.7 (NA)	--

n: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval included for doses that were demonstrated to be effective; NA: not available.

[a] Difference (drug minus placebo) in least-squares estimates with respect to the primary efficacy parameter. For Trial 1, it refers to the mean score at the endpoint visit; for Trials 2 and 3, it refers to the mean change from baseline to the endpoint visit.

[b] Doses that are demonstrated to be statistically significantly superior to placebo.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, trials have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions, i.e., bupropion sustained-release 150 mg twice daily was shown to be

bioequivalent to 100 mg 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

In a longer-term trial, 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 twice daily) were randomized to continuation of their same dose of WELLBUTRIN SR or placebo for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued treatment with WELLBUTRIN SR experienced significantly lower relapse rates over the subsequent 44 weeks compared with those receiving placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

WELLBUTRIN SR Sustained-Release Tablets, 100 mg of bupropion hydrochloride, are blue, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 100" in bottles of 60 (NDC 0173-0947-55) tablets.

WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of 60 (NDC 0173-0135-55) tablets.

WELLBUTRIN SR Sustained-Release Tablets, 200 mg of bupropion hydrochloride, are light pink, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 200" in bottles of 60 (NDC 0173-0722-00) tablets.

Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with WELLBUTRIN SR and counsel them in its appropriate use.

A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions," "Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions," and "What Other Important Information Should I Know About WELLBUTRIN SR?" is available for WELLBUTRIN SR. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Advise patients regarding the following issues and to alert their prescriber if these occur while taking WELLBUTRIN SR.

Suicidal Thoughts and Behaviors: Instruct patients, their families, and/or their caregivers to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Advise families and caregivers of patients to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or healthcare professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment: Although WELLBUTRIN SR is not indicated for smoking cessation treatment, it contains the same active ingredient as ZYBAN which is approved for this use. Advise patients, families and caregivers that quitting smoking, with or without ZYBAN, may trigger nicotine withdrawal symptoms (e.g., including depression or agitation), or worsen pre-existing psychiatric illness. Some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

Severe Allergic Reactions: Educate patients on the symptoms of hypersensitivity and to discontinue WELLBUTRIN SR if they have a severe allergic reaction.

Seizure: Instruct patients to discontinue and not restart WELLBUTRIN SR if they experience a seizure while on treatment. Advise patients that the excessive use or abrupt discontinuation of alcohol, benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure. Advise patients to minimize or avoid use of alcohol.

As the dose is increased during initial titration to doses above 150 mg per day, instruct patients to take WELLBUTRIN SR in 2 divided doses, preferably with at least 8 hours between successive doses, to minimize the risk of seizures.

Bupropion-Containing Products: Educate patients that WELLBUTRIN SR contains the same active ingredient (bupropion hydrochloride) found in ZYBAN, which is used as an aid to smoking cessation treatment, and that WELLBUTRIN SR should not be used in combination with ZYBAN or any other medications that contain bupropion (such as WELLBUTRIN®, the immediate-release formulation and WELLBUTRIN XL® or FORFIVO XL™, the extended-release formulations, and APLENZIN®, the extended-release formulation of bupropion hydrobromide). In addition, there are a number of generic bupropion HCl products for the immediate-, sustained-, and extended-release formulations.

Potential for Cognitive and Motor Impairment: Advise patients that any CNS-active drug like WELLBUTRIN SR may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Advise patients that until they are reasonably certain that WELLBUTRIN SR does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. WELLBUTRIN SR may lead to decreased alcohol tolerance.

Concomitant Medications: Counsel patients to notify their healthcare provider if they are taking or plan to take any prescription or over-the-counter drugs because WELLBUTRIN SR Sustained-Release Tablets and other drugs may affect each others' metabolisms.

Pregnancy: Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

Precautions for Nursing Mothers: Advise patients that WELLBUTRIN SR is present in human milk in small amounts.

Storage Information: Instruct patients to store WELLBUTRIN SR at room temperature, between 59°F and 86°F (15°C to 30°C) and keep the tablets dry and out of the light.

Administration Information: Instruct patients to swallow WELLBUTRIN SR Tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets; they are designed to slowly release drug in the body. When patients take more than 150 mg per day, instruct them to take WELLBUTRIN SR in 2 doses at least 8 hours apart, to minimize the risk of seizures. Instruct patients if they miss a dose, not to take an extra tablet to make up for the missed dose and to take the next tablet at the regular time because of the dose-related risk of seizure. Instruct patients that WELLBUTRIN SR Tablets may have an odor. WELLBUTRIN SR can be taken with or without food.

Manufactured for:

GlaxoSmithKline
Research Triangle Park, NC 27709

WLT:XPI

MEDICATION GUIDE
WELLBUTRIN® SR (WELL byu-trin)
(bupropion hydrochloride) Sustained-Release Tablets

Read this Medication Guide carefully before you start taking WELLBUTRIN SR and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment. If you have any questions about WELLBUTRIN SR, ask your healthcare provider or pharmacist.

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to quit smoking; and the third section is entitled "What Other Important Information Should I Know About WELLBUTRIN SR?"

Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your healthcare provider or your family member's healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**
2. **Depression or other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

It is not known if WELLBUTRIN SR is safe and effective in children under the age of 18.

Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking.

Although WELLBUTRIN SR is not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN® which is used to help patients quit smoking.

Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking bupropion to help them quit smoking. These symptoms can develop during treatment with bupropion or after stopping treatment with bupropion.

If you, your family member, or your caregiver notice agitation, hostility, depression, or changes in thinking or behavior that are not typical for you, or you have any of the following symptoms, stop taking bupropion and call your healthcare provider right away:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without bupropion, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit

smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking bupropion, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without bupropion.

What Other Important Information Should I Know About WELLBUTRIN SR?

- **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN SR, especially in people:**
  - with certain medical problems.
  - who take certain medicines.

  The chance of having seizures increases with higher doses of WELLBUTRIN SR. For more information, see the sections "Who should not take WELLBUTRIN SR?" and "What should I tell my healthcare provider before taking WELLBUTRIN SR?" Tell your healthcare provider about all of your medical conditions and all the medicines you take. **Do not take any other medicines while you are taking WELLBUTRIN SR unless your healthcare provider has said it is okay to take them.**

  If you have a seizure while taking WELLBUTRIN SR, stop taking the tablets and call your healthcare provider right away. Do not take WELLBUTRIN SR again if you have a seizure.

- **High blood pressure (hypertension). Some people get high blood pressure, that can be severe, while taking WELLBUTRIN SR.** The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.
- **Manic episodes.** Some people may have periods of mania while taking WELLBUTRIN SR, including:
  - Greatly increased energy
  - Severe trouble sleeping
  - Racing thoughts
  - Reckless behavior
  - Unusually grand ideas
  - Excessive happiness or irritability
  - Talking more or faster than usual

If you have any of the above symptoms of mania, call your healthcare provider.

- **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your healthcare provider.
- **Severe allergic reactions. Some people can have severe allergic reactions to WELLBUTRIN SR. Stop taking WELLBUTRIN SR and call your healthcare provider right away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious allergic reaction.

What is WELLBUTRIN SR?

WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take WELLBUTRIN SR?

Do not take WELLBUTRIN SR if you

- have or had a seizure disorder or epilepsy.
- have or had an eating disorder such as anorexia nervosa or bulimia.
- **are taking any other medicines that contain bupropion, ZYBAN (used to help people stop smoking) APLENZIN®, FORFIVO XL™, WELLBUTRIN®, or WELLBUTRIN XL®.**Bupropion is the same active ingredient that is in WELLBUTRIN SR.
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines, and you stop using them all of a sudden.
- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
  - do not take an MAOI within 2 weeks of stopping WELLBUTRIN SR unless directed to do so by your healthcare provider.
  - do not start WELLBUTRIN SR if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your healthcare provider.
- are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the inactive ingredients. See the end of this Medication Guide for a complete list of ingredients in WELLBUTRIN SR.

What should I tell my healthcare provider before taking WELLBUTRIN SR?

Tell your healthcare provider if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions."

Tell your healthcare provider about your other medical conditions including if you:

- have liver problems, especially cirrhosis of the liver.
- have kidney problems.
- have, or have had, an eating disorder, such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink alcohol.
- abuse prescription medicines or street drugs.
- are pregnant or plan to become pregnant.
- are breastfeeding. WELLBUTRIN passes into your milk in small amounts.

Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or other serious side effects if you take them while you are taking WELLBUTRIN SR.

How should I take WELLBUTRIN SR?

- Take WELLBUTRIN SR exactly as prescribed by your healthcare provider.
- **Swallow WELLBUTRIN SR Tablets whole. Do not chew, cut, or crush WELLBUTRIN SR Tablets.** If you do, the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. **Tell your healthcare provider if you cannot swallow tablets.**
- Take WELLBUTRIN SR at the same time each day.
- Take your doses of WELLBUTRIN SR at least 8 hours apart.
- You may take WELLBUTRIN SR with or without food.
- If you miss a dose, do not take an extra dose to make up for the dose you missed. Wait and take your next dose at the regular time. **This is very important.** Too much WELLBUTRIN SR can increase your chance of having a seizure.
- If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or poison control center right away.

- **Do not take any other medicines while taking WELLBUTRIN SR unless your healthcare provider has told you it is okay.**
- If you are taking WELLBUTRIN SR for the treatment of major depressive disorder, it may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel better, it is important to keep taking WELLBUTRIN SR exactly as directed by your healthcare provider. Call your healthcare provider if you do not feel WELLBUTRIN SR is working for you.
- Do not change your dose or stop taking WELLBUTRIN SR without talking with your healthcare provider first.

What should I avoid while taking WELLBUTRIN SR?

- Limit or avoid using alcohol during treatment with WELLBUTRIN SR. If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.
- Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects you. WELLBUTRIN SR can affect your ability to do these things safely.

What are possible side effects of WELLBUTRIN SR?

See **"What Other Important Information Should I Know About WELLBUTRIN SR?"**

WELLBUTRIN SR can cause serious side effects.

The most common side effects of WELLBUTRIN SR include:

- Headache
- Dry mouth
- Nausea
- Trouble sleeping
- Dizziness
- Sore throat
- Constipation

If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your medicine too close to bedtime.

Tell your healthcare provider right away about any side effects that bother you.

These are not all the possible side effects of WELLBUTRIN SR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

How should I store WELLBUTRIN SR?

- Store WELLBUTRIN SR at room temperature between 59°F and 86°F (15°C to 30°C).
- Keep WELLBUTRIN SR dry and out of the light.
- WELLBUTRIN SR Tablets may have an odor.

Keep WELLBUTRIN SR and all medicines out of the reach of children.

General Information about WELLBUTRIN SR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELLBUTRIN SR for a condition for which it was not prescribed. Do not give WELLBUTRIN SR to other people, even if they have the same symptoms you have. It may harm them.

If you take a urine drug screening test, WELLBUTRIN SR may make the test result positive for amphetamines. If you tell the person giving you the drug screening test that you are taking WELLBUTRIN SR, they can do a more specific drug screening test that should not have this problem.

This Medication Guide summarizes important information about WELLBUTRIN SR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about WELLBUTRIN SR that is written for healthcare professionals.

For more information about WELLBUTRIN SR, go to www.wellbutrin.com or call 1-888-825-5249.

What are the ingredients in WELLBUTRIN SR?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake,

and the 200-mg tablet contains FD&C Red No. 40 Lake. The tablets are printed with edible black ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:

GlaxoSmithKline
Research Triangle Park, NC 27709

Month Year
WLS: MG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA/Supplement#:	018644/S-047; 020358/S-054
Drug Name:	Wellbutrin®;Wellbutrin SR® bupropion hydrochloride
Dosage Forms:	IR Tablet; SR Tablet
Sponsor:	GSK
Indication:	MDD
Submission Date:	Dec. 11, 2012
Review Type:	Prior Approval Supplement
OCP Reviewer Team:	Huixia Zhang, Ph.D., Hao Zhu, Ph.D.

Memorandum

Bupropion hydrochloride immediate release (IR) formulation was first approved for major depressive disorder on 12/30/1985 under the trade name of Wellbutrin®. Subsequently, the sustained release (SR) formulation was approved on 10/4/1996 under the trade name of Wellbutrin SR®. In the Agency's correspondence letter dated Oct 11, 2012, the sponsor was requested to convert the labels of the two products into Physician Labeling Rule (PLR) format. The currently submitted supplemental applications (S-047 for NDA 018644 and S-054 for NDA 020358) include the sponsor's proposed labels to meet the request.

This memo summarizes two major changes related to clinical pharmacology in Wellbutrin® and Wellbutrin SR® labels.

1) Wellbutrin® label: Drug administration with regard to food

In the existing Wellbutrin® label, the medication guide states that "WELLBUTRIN® can be taken with or without food", while no instruction with regard to food is given under the dosage and administration section. In addition, no food effect study is described under the Clinical Pharmacology section. The sponsor confirmed that no study was conducted to evaluate the food effect on the bupropion hydrochloride IR formulation. Because no specific food effect study was conducted to support the statement under the current medication guide section, our typical practice is to remove the statement from the label. However, the current Wellbutrin® medication guide has been effective since 2002-2005 (Paul David email dated 5/24/2013). Since then, the division of psychiatry products (DPP) has not been notified any increased incidence of adverse events related to food intake from the post-market experiences. Furthermore, Wellbutrin SR® and Wellbutrin XL® formulations showed no clinically meaningful food effect from the dedicated food effect studies. Thus, clinically significant food effect for the IR formulation is unlikely. Hence, we are comfortable to allow patients taking Wellbutrin IR formulation without regard to food and the following statement is recommended in Section 2.1 "General Use Instruction": WELLBUTRIN may be taken with or without food. It is to note that the

rationales provided in this review are only applicable to Wellbutrin® and should not be generalized to other products.

2) Wellbutrin® and Wellbutrin SR ® label: Dose adjustment in patients concomitantly taking CYP2B6 inhibitors

In Section 7, "Drug Interactions", the following language is recommended when inhibitors of CYP2B6 are coadministered with Wellbutrin product:

Inhibitors of CYP2B6: *Ticlopidine and Clopidogrel:* Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of WELLBUTRIN SR may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) *[see Clinical Pharmacology (12.3)]*.

(b) (4)

According to the approved label, hydroxybupropion is one of the three major active metabolites of bupropion, and its formation is mainly mediated by CYP2B6. At steady state, AUC of hydroxybupropion is about 17-times that of bupropion, (b) (4)

Bupropion-containing products can cause seizure, the major safety concern, in a non-linear dose-dependent manner. In clinical studies using bupropion hydrochloride sustained-release formulation up to 300 mg/day, the incidence of seizure was approximately 0.1% (Wellbutrin® and Wellbutrin SR® label). The seizure incidence was approximately 0.4% with bupropion hydrochloride immediate-release formulation in the dose range of 300 mg to 450 mg (Wellbutrin® and Wellbutrin SR® label). Additional data accumulated for bupropion IR formulation in human suggests that the estimated seizure incidence increases almost 10-fold between the dose of 450 and 600 mg/day (Wellbutrin® and Wellbutrin SR® label).

The convulsive liability of bupropion and its major metabolites was assessed in female Swiss albino mice following intraperitoneal administration (Silverstone et al., 2008). The actual doses of the metabolites administered to mice were equimolar equivalents of bupropion hydrochloride 25, 50 and 75 mg/kg. It was found that all three metabolites were associated with a greater percentage of seizures compared to bupropion. Hydroxybupropion hydrochloride treatment induced the largest percentage of convulsing mice (100% at both 50 and 75 mg/kg), compared to bupropion hydrochloride (0% and 10% at 50 and 75 mg/kg). This finding suggested that hydroxybupropion is likely to be a more potent convulsant than the parent drug,

given the caveats that the animal study did not include pharmacokinetic assessment and the study was conducted only in mice.

It was reported in the literature (Turpeinen et al.,2005) that concomitant treatment with CYP2B6 inhibitors clopidogrel or ticlopidine increased bupropion exposure by 60% and 85%, respectively, but decreased hydroxybupropion exposure by 52% and 84%, respectively. These study results were reviewed and integrated into Forvivo XL (bupropion hydrochloride extended-release tablets) label (Dr. Bei Yu, review dated 1/25/2010 in DARRTS). (b) (4)

[redacted]

References:

1. Turpeinen M, Tolonen A, Uusitalo J, Jalonen J, Pelkonen O, Laine K(2005) Effect of clopidogrel and ticlopidine on cytochrome P450 2B6 activity as measured by bupropion hydroxylation. Clin Pharmacol Ther. 77(6):553-9.

2. Silverstone PH, Williams R, McMahon L, Fleming R, Fogarty S (2008) Convulsive liability of bupropion hydrochloride metabolites in Swiss albino mice. Ann Gen Psychiatry 7:19-27

SIGNATURES

Huixia Zhang, Ph.D.
Reviewer, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

RD/FT, Initialized by Hao Zhu, Ph.D.
Team Leader, Psychiatry Drug Team, DCP1
Office of Clinical Pharmacology

Cc: NDA018644/S-047
NDA020358/S-054
DCP1 (Mehta, Uppoor, Zhu, Zhang)

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/s/

HUIXIA ZHANG
12/13/2013

HAO ZHU
12/13/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: December 19, 2013
Drug (NDA): Wellbutrin (bupropion hydrochloride) 75 mg and 100 mg Tablets (NDA 18644) and Wellbutrin SR (bupropion hydrochloride) Sustained-Release 100 mg, 150 mg, and 200 mg Tablets (NDA 20358)
Sponsor: GlaxoSmithKline
Indication: Major Depressive Disorder

Supplements under review:

NDA	Supplement	Received	Proposed Action
Wellbutrin (bupropion hydrochloride) (NDA 18644)			
018644	SLR-045	04-05-2012	Approved 03-19-2013
018644	SLR-046	11-30-2012	Open
018644	SLR-047	12-12-2012	Open
Wellbutrin SR (buproprion hydrochloride) Sustained-Release (NDA 20358)			
020358	SLR-052	04-05-2012	Approved 03-19-2013
020358	SLR-053	11-30-2012	Open
020358	SLR-054	12-12-2012	Open

BACKGROUND

1. Last approved labeling is dated March 19, 2013 for Wellbutrin (NDA 18644/S-045) and Wellbutrin SR (NDA 20358/S-052).
2. Prior Approval Labeling Supplements NDA 18644/S-046 and 20358/S-053, submitted on November 30, 2012, proposed draft labeling revisions to the (b) (4) updating the information about use during pregnancy (b) (4) We sent a Complete Response letter on May 28, 2013 with reasons for this action and labeling updates. The sponsor resubmitted the labeling supplements on June 21, 2013.
3. In response to the Agency request dated October 11, 2012, to submit an updated label to comply with Physician Labeling Rule (PLR) regulations, the sponsor submitted prior approval labeling supplements NDA 18644/S-046 and 20358/S-054 on December 12, 2012 with a proposed label in PLR format. We coordinated with DAAAP and internally to ensure all bupropion labels are consistent.

REVIEW

NDA 18644/S-046 and NDA 20358/S-053
CBE: No
Reviewed by Medical Officer: Yes (Maternal Health Consult Review dated 7/19/2013)

This prior approval labeling supplement changes the following language in the Highlights (HL), Section 8.1 Pregnancy, Section 8.3 Nursing Mothers, and Section 17 Patient Counseling. Final agreed-upon edits are tracked over the sponsor's proposed language, dated June 21, 2013.

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

(b) (4)

[redacted]

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(b) (4)

17.8 Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

17.9 Precautions for Nursing Mothers

Advise patients that bupropion is secreted in human milk. (b) (4)

REVIEW

NDA 18644/S-047 and 20358/S-054
CBE: No
Reviewed by Medical Officer: Yes

Labeling updates were made throughout the label as part of the PLR conversion. A summary of the main major changes include:

- Updated Boxed Warning for all bupropion products.
- Added "Children" to the title of Section 5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults and the Table of Contents.
- Kept the statement "WELLBUTRIN may be taken with or without food". Although there were no dedicated food studies done with Wellbutrin IR, this statement has been in the label since 2006 and possibly earlier. The sponsor also provided justification to support that the drug is classified as BCS 1, high permeability, high solubility, thus bioavailability would unlikely be affected by food.
- Added "(Glomerular Filtration Rate <90 mL/min)" to provide information about the inclusion criteria for the Renal Impairment study.
- Section 7 Drug Interactions:
    - Removed "Dose reduction of WELLBUTRIN may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel)" because the major active moiety OH-Bupropion AUC was decreased by 52-84% after clopidogrel or ticlopidine administration. Though bupropion exposure was

increased, the overall effective exposure was decreased. Dose reduction is not justified. Clinicians should monitor patients for the drug interaction and adjust the dose of bupropion accordingly.

- Added "The exposures (Cmax and AUC) of hydroxybupropion were decreased 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine." To Section 12.3 Pharmacokinetics Drug Interactions subsection.

- Updated Section 8.1 Pregnancy and Section 8.3 Nursing Mothers, per MHT's recommendations and update the format of the label in anticipation of the Pregnancy Rule.
- Updated Section 16 and updated Section 17 and Medication Guide accordingly.
- Updated Section 17 according to Draft Guidance for Industry: Patient Counseling Information 846 Section of Labeling for Human Prescription Drug and Biological Products – Content and 847 Format, September 2013.
- Updates to the PI and MG per the recommendations of DMPP Patient Labeling Reviewer (review dated 5/23/2013) and OPDP Labeling Reviewer (review dated 6/3/2013).

CONCLUSIONS

1. A side by side review found no changes other than those specified by the sponsor and provides for the above labeling changes when compared to the last approved labeling for Wellbutrin and Wellbutrin SR.

2. I recommend that we approve the agreed-upon updated Wellbutrin and Wellbutrin SR labels for NDA 18644/S-046/S-047 and NDA 20358/S-053/S-054.

{See appended electronic signature page}
CDR Juliette Touré, Pharm.D.
Senior Regulatory Project Manager

{See appended electronic signature page}
CAPT Paul David, R.Ph., CPMS

Attachment: Annotated labeling

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/s/

JULIETTE T TOURE
12/20/2013

PAUL A DAVID
12/22/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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PEDIATRIC AND MATERNAL HEALTH STAFF, MATERNAL HEALTH TEAM REVIEW

Date: 07-16-2013

From: Leyla Sahin, M.D.
Medical Officer,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Melissa S Tassinari, PhD.
Acting Team Leader,
Pediatric and Maternal Health Staff, Maternal Health Team

Through: Lynne P Yao, M.D.
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Psychiatry Products

Drug: Wellbutrin (bupropion hydrochloride); NDA 18644

Applicant: GlaxoSmithKline

Subject: New case control study on bupropion exposure in pregnancy and risk of cardiac defects; Pregnancy Labeling

Materials Reviewed: Applicant labeling and justification document, literature review

Consult Question: Please review the new study report and proposed labeling changes to the Pregnancy section.

EXECUTIVE SUMMARY

Since bupropion was approved in 1985, the cumulative data have not demonstrated an association with its use in pregnancy and the development of major congenital malformations. These data include the final report from the manufacturer's pregnancy registry, and both published and unpublished epidemiologic studies. There were conflicting results from these studies regarding the risk of specific cardiovascular defects, but these studies were limited by recall bias, a small number of exposed cases, and bias due to multiplicity of testing in case control studies. Therefore an increased risk for specific cardiovascular defects following bupropion exposure during pregnancy could not be established (b) (4) Pregnancy labeling should also be updated to reflect available data in a manner that is clinically relevant for prescribers and healthcare providers.

INTRODUCTION

GlaxoSmithKline submitted a prior approval labeling supplement for Wellbutrin (bupropion) and (b) (4) based on results from a new study and their assessment of the cumulative data. The Division of Psychiatry Products (DPP) requested the Pediatric and Maternal Health Staff, Maternal Health Team's (PMHS-MHT) review of the applicant's submission and proposed labeling for Pregnancy for Wellbutrin, in an effort to update labeling for all bupropion products. In addition, subsequent to the proposal to modify the pregnancy section of Wellbutrin labeling, the applicant submitted a prior approval labeling supplement to convert labeling to the Physician Labeling Rule (PLR) format. PMHS-MHT reviewed available new data on use of bupropion in pregnancy in collaboration with the Office of Surveillance and Epidemiology's Division of Epidemiology (DEPI) I. This review summarizes available data, and provides conclusions and recommendations regarding Pregnancy and Nursing Mothers labeling for Wellbutrin and other bupropion products.

BACKGROUND

Bupropion is an aminoketone antidepressant that is unrelated to tricyclic, tetracyclic, selective serotonin reuptake inhibitors, or other antidepressant agents. It is approved for the adult treatment of depression, seasonal affective disorder, and for smoking cessation.

GlaxoSmithKline (GSK) submitted a case control study conducted by the Slone Epidemiology Center at Boston University that evaluated cardiac birth defects. This study was commissioned by the manufacturer in order to assess the risk for previously reported cardiac birth defects following exposure to bupropion in the first trimester of pregnancy. A case control study by the Centers for Disease Control's (CDC) National Birth Defects Prevention Study (NBDPS)[1] found an association between bupropion use in the first trimester and an increased risk for left ventricular outflow tract obstruction (LVOTO), a group of cardiovascular malformations that

[1] Alwan S, Reefhuis J, Botto LD et al. Maternal use of Bupropion and risk for congenital heart defects. Am J Obstet Gynecol. 2010; 203:52e1-6.

includes defects such as aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart syndrome.[2] A retrospective cohort study by GSK that used United Healthcare claims data[3] found no increase in the risk of cardiovascular malformations in infants exposed to bupropion during the first trimester of pregnancy when compared to background prevalence or to mothers exposed to other antidepressants during the first trimester. A subsequent reanalysis of data from the original retrospective cohort study by GSK was underpowered to assess LVOTO.

The following is a summary of previous reviews by PMHS-MHT:

- Review of final bupropion pregnancy registry study report by Richardae Araojo, PharmD (review dated 10-8-2008).

- Review of applicant's reanalysis of left ventricular outflow tract obstruction (LVOTO) outcome in a previous retrospective cohort study and literature review by Upasana Bhatnagar, MD (review dated 11-28-2011)

- Review of pregnancy and lactation labeling by Upasana Bhatnagar, MD (review dated 03-09-2012). These labeling recommendations were incorporated into the Aplenzin (bupropion hydrobromide) labeling August 15, 2012.

REVIEW OF STUDY

Louik C and (b) (4) First Trimester Exposure to Bupropion in Relation to the Risk of Cardiac Defects. A report from GlaxoSmithkline by Slone Epidemiology Center at Boston University. 11 July 2012.

Objective

The objective of the study was to assess the association between bupropion use during the first trimester of pregnancy and cardiac defects, and specifically to test the previously reported association with left outflow tract defects.[1]

Primary outcomes were the following:

- ventricular septal defects (VSD)
- left outflow tract defects
- coarctation of aorta
- hypoplastic left heart syndrome.

[2] Botto LD, Lin AE, Riehle-Colarusso T, et al. Seeking Causes: Classifying and Evaluating Congenital Heart Defects in Etiologic Studies. Birth Defects Res A Clin Mol Teratol. 2007; 79: 714-727.

[3] Cole JA, Modell JG, Haight BR, et al. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiology and Drug Safety. 2007; 16: 474-484.

Methods

The authors conducted a case control study using data from the Slone Epidemiology Birth Defect Study (BDS), a multi-center program of case-control surveillance for birth defects. This study was initiated in 1976 and identifies birth defects at study centers in the following locations: areas surrounding Boston, Philadelphia, Toronto (through 2003), and San Diego (since 2000), as well as a portion of New York State (since 2004) and the entire state of Massachusetts (since 1998). In Philadelphia, Toronto, and San Diego, birth defects are identified by reviewing hospital admission and discharge records. Statewide birth defect registries are used to identify patients in New York and Massachusetts. Minor defects are excluded. As of 1992, the BDS began enrolling mothers of non-malformed infants at participating hospitals and since 1998, a population-based random sample of mothers were enrolled from Massachusetts.

Within six months of delivery, women are interviewed for 45-60 minutes by phone interview by a trained nurse unaware of the study hypotheses. Data is collected on demographics, reproductive and medical factors, health behaviors such as cigarette smoking, alcohol, and caffeine consumption, occupational exposure, and dietary intake. Information on medication exposure and medical conditions is obtained. All women sign a medical release form in order to confirm outcomes with medical records.

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). Covariates listed below were entered into the crude model individually, and risk factors changing the point estimate by ≥10% were retained in the final model.

Covariates

To assess confounding, the following risk factors were assessed: maternal age, maternal race, maternal education, LMP year, study center, smoking history, alcohol consumption, family history of birth defects, family history of any cardiac defect in a first degree relative, pre-pregnant body mass index, gravidity, history of seizures, diabetes mellitus, hypertension, infertility, and periconceptional folic acid use.

Results

The study included 7,913 case infants with cardiac defects and 8,611 control infants without defects.

Use of bupropion in the first trimester was associated with an increased risk of VSD (adjusted OR=2.5; 95%CI: 1.3-5.0), based on 17 exposed cases. Use of bupropion with another antidepressant did not have a significant association with VSD. Bupropion did not have a significant association with any other type of cardiac defect, including LVOTO (adjusted OR=0.4; 95% CI: 0.1-1.6). There were only 2 exposed cases in the LVOTO group.

Because there were few exposed cases in each outcome group, the investigators were limited in their ability to consider multiple confounders simultaneously. The authors acknowledge that there may be therefore be residual confounding in their study results.

Authors' Conclusions

The authors concluded that their study found an increased risk for VSD with use of bupropion alone. However, they also note that there was no increase in risk for VSD when bupropion was used in combination with other antidepressants, and that it is possible that their positive finding may be a chance finding.

They did not find an increased risk for LVOTO as was seen in the NBDPS[1]; however they commented that their study results are based on only two exposed cases.

Reviewer's Comments

This study did not confirm the NBDPS finding that showed an association between use of bupropion in the first trimester and LVOTO. However, the current study result is limited by the small number of exposed cases (n=2).

This study found that bupropion use in the first trimester is associated with VSD. As noted by the authors of the study, there was no association between use of bupropion in combination with other antidepressants and VSD, and the authors state that the association with VSD may be a chance finding. Some of the limitations of this study include the potential for recall bias and residual confounding; therefore it is not possible to draw clear conclusions from this study.

Bupropion Use in Pregnancy Literature Review

There are no new published studies on the use of bupropion in pregnancy since the last PMHS-MHT literature review dated 11-28-2011.

LABELING

Bupropion is labeled pregnancy category C based on adverse developmental effects in the rabbit at exposures similar to the recommended human dose. Current Wellbutrin labeling contains a description of the United Healthcare database retrospective cohort study, which showed no increased risk for malformations overall or for cardiovascular malformations overall, following first trimester exposure to bupropion (see Appendix B for current labeling). In the current submission the applicant proposes (b) (4) See Appendix C for applicant's proposed labeling.

Reviewer's Comments

(b) (4) *See Appendix E for labeling recommendations.*

Current labeling for Wellbutrin does not contain any information on use during lactation. PMHS-MHT previously reviewed available bupropion lactation data and provided labeling recommendations which were incorporated into Aplenzin (bupropion hydrobromide) labeling in August 2012 (see Appendix D). Wellbutrin Nursing Mothers section of labeling should be revised to include the lactation data incorporated into Aplenzin labeling.

DISCUSSION AND CONCLUSIONS

Since bupropion's approval in 1985, there has been an accumulation of published and unpublished data on birth defects following the use of bupropion in pregnancy. Data that have been previously reviewed by PMHS-MHT and DEPI include the final bupropion pregnancy registry report, a CDC NBDPS case-control study, a United Healthcare database retrospective cohort study, and a small prospective cohort study. New data from the Slone Epidemiology Center do not corroborate the NBDPS finding that demonstrated a statistically significant association between use of bupropion in the first trimester and LVOTO. However this result is limited by the small number of exposed cases (n=2). The Slone Epidemiology study also found that bupropion use in the first trimester is associated with VSD, but not when used in combination with other antidepressants. This finding is somewhat contradictory and may be related to inherent limitations of the study.

PMHS-MHT collaborated with Dr. Steven Bird, epidemiologist in OSE's DEPI I and DPP regarding the cumulative data. The cumulative data on the risk of congenital malformations overall, based on epidemiological studies of pregnant women exposed to bupropion in the first trimester, are consistent across studies and indicate no increased risk. Some of these studies present conflicting results regarding the risk of specific cardiovascular defects (LVOTO and VSD), and in our assessment of these studies an increased risk for specific cardiovascular defects following bupropion exposure during pregnancy could not be determined (see Appendix A for summary of study findings). Therefore this information should (b) (4) be included under Data. In concurrence with DPP and DEPI I, PMHS-MHT agrees that available data (b) (4) In addition, PMHS-MHT concludes that the current regulatory language under Pregnancy, "WELLBUTRIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" adequately reflects the risk –benefit profile regarding use in pregnancy.

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers labeling information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during

pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the labeling, not the amount.

In collaboration with DEPI I, PMHS-MHT developed language for the human data section of the pregnancy labeling for bupropion in the format of the proposed PLLR to provide an assessment of available data and communication of this information in a manner that is clinically relevant for healthcare providers (see Appendix E). The labeling recommendations incorporate revisions that were made to Aplenzin (bupropion hydrobromide) labeling August 15, 2012 (see Appendix D).

PMHS-MHT previously reviewed available bupropion lactation data and provided labeling recommendations which were incorporated into Aplenzin labeling in August 2012 (see Appendix D). Wellbutrin Nursing Mothers section of labeling should be revised to include the lactation data.

RECOMMENDATIONS

1. (b) (4)

2. Add new human data on exposure in pregnancy to labeling (see Appendix E).

3. Revise the Nursing Mothers section of labeling so that it is consistent with Aplenzin labeling.

APPENDIX A

Summary of Bupropion Birth Defect Studies

Studies that showed no increased risk of birth defects, based on outcome

Birth defects overall

1. Bupropion pregnancy registry[4]
   n=675 1st trimester bupropion exposures

2. United Healthcare database study (retrospective cohort study)
   n=1,213 1st trimester bupropion exposures

3. Motherisk prospective cohort study[5]
   n=91 1st trimester bupropion exposures, compared to 89 exposures to other antidepressants, 89 exposures to nonteratogens

Cardiovascular defects as a group

1. United Healthcare database study (retrospective cohort study)

2. National Birth Defects Prevention Study (NBDPS) case control study
   n=6,853 infants with cardiac defects and 5,763 with noncardiac defects

Left Ventricular Outflow Tract Obstruction (LVOTO)

1. Slone Epidemiology case control study
   n=7,913 infant cases of cardiac defects and 8,611 control infants
   LVOTO: n = 2; adjusted OR = 0.4; 95% CI: 0.1, 1.6

Studies that showed an increased risk of specific birth defects, based on outcome

LVOTO

1. NBDPS case control study
   LVOTO: n = 10; adjusted OR = 2.6; 95% CI: 1.2, 5.7

Ventricular Septal Defect (VSD)

1. Slone Epidemiology case control study
   n=7,913 infant cases of cardiac defects and 8,611 control infants
   VSD: n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0

[4] The bupropion pregnancy registry final report: 1 September 1997 through 31 March 2008. Wilmington NC, 2008.

[5] Chun-Fai-Chan B, Koren G, Fayez I et al. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. American Journal of Obstetrics and Gynecology. 2005; 192:932-6.

APPENDIX B
Current approved Wellbutrin Labeling – Pregnancy and Nursing Mothers

The following is current approved labeling for Wellbutrin:

PRECAUTIONS
Teratogenic Effects: **Pregnancy Category C.** In studies conducted in rats and rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater.
When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.
One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. WELLBUTRIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of WELLBUTRIN on labor and delivery in humans is unknown.

Nursing Mothers
Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

APPENDIX C
Applicant's proposed labeling for Pregnancy and Nursing Mothers

The following is the applicant's proposed labeling for Wellbutrin:

(b) (4)

1 Page Immediately Following Withheld - b(4) Draft Labeling

APPENDIX D
Current Approved Aplenzin (bupropion hydrobromide) Pregnancy and Nursing Mothers labeling (revised August 15, 2012)

Pregnancy Category C

Risk Summary

Data from epidemiological studies including pregnant women indicate no increased risk of congenital malformations with APLENZIN exposure in pregnancy. Data regarding the risk of congenital cardiovascular malformations with first trimester bupropion exposure is inconsistent. No clear evidence of teratogenicity was observed in reproductive developmental studies conducted in rats and rabbits. However, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m2 basis) and greater and decreased fetal weights were seen at 50 mg/kg and greater. APLENZIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Human Data

Data from a retrospective cohort study using the United Healthcare database (1213 infants exposed to bupropion in the first trimester) demonstrated no greater risk for congenital malformations overall or cardiovascular malformations specifically after first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or to bupropion exposure outside of the first trimester. A retrospective case-controlled study included 6853 infants with cardiac defects and 5753 with noncardiac defects from the National Birth Defects Prevention Study. This study found an association between infants with left outflow tract defects (LVOTO) with maternal bupropion use but not among infants with other types of heart defects or six other noncardiac defect categories. A subsequent reanalysis of the United Healthcare database, to assess the risk of cardiovascular malformations, particularly LVOTO, lacked adequate power to detect an increased risk.

Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m2 basis) and greater. Decreased fetal weights were observed at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

APPENDIX E
LABELING RECOMMENDATIONS for Pregnancy and Nursing Mothers

Labeling appears in PLR format as a prior approval labeling supplement for PLR conversion was submitted by the applicant subsequent to their initial submission. Labeling also incorporates revisions to Aplenzin (bupropion hydrobromide) labeling that were approved August 15, 2012 (see Appendix D).
The following revisions were agreed upon by PMHS-MHT, DPP and DEpi I.

----------**USE IN SPECIFIC POPULATIONS**----------

- Pregnancy: Use only if the benefit outweighs potential risk to the fetus (8.1)

(b) (4)

(b) (4)

[redacted]

17 PATIENT COUNSELING INFORMATION

17.8 Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

17.9 Precautions for Nursing Mothers

Advise patients that bupropion is present in human milk in small amounts.

MEDICATION GUIDE

Tell your healthcare provider about your other medical conditions including if you:

- are pregnant or plan to become pregnant.
- are breastfeeding. WELLBUTRIN passes into your milk in small amounts.

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/s/

LEYLA SAHIN
07/16/2013

MELISSA S TASSINARI
07/16/2013

LYNNE P YAO
07/19/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **June 3, 2013**

To: Juliette Touré, PharmD
Senior Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Mathilda Fienkeng, PharmD
Team Leader, OPDP

Subject: **NDA #018644**
Wellbutrin® (bupropion hydrochloride) Tablets
NDA # 020358
Wellbutrin SR® (bupropion hydrochloride) Sustained-Release Tablets
(b) (4)

OPDP has reviewed the draft product labeling (PI) and medication guide (MG) for Wellbutrin® (bupropion hydrochloride) Tablets as requested in the consult from DPP dated May 13, 2013.

OPDP's comments on the draft PI for Wellbutrin are based on the version posted by Juliette Touré in the eroom (http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_b8e6b), dated May 23, 2013. OPDP's comments on the draft MG are based on the review completed by Sharon Williams, DMPP on May, 23, 2013. Comments are provided directly on the draft PI and MG below. These comments should also be applied to the draft labeling for Wellbutrin SR (b) (4) and we will provide comments under separate cover on the draft labeling for Wellbutrin SR (b) (4) when the substantially complete labels are available.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

36 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

SUSANNAH O'DONNELL
06/03/2013

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**May 23, 2013**
To:	Mitchell Mathis, MD Acting Director **Division of Psychiatry Products (DPP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, RN, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon W. Williams, MSN, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling Medication Guide (MG)
Drug Name (established name):	WELLBUTRIN (bupropion hydrochloride) WELLBUTRIN SR (bupropion hydrochloride) (b) (4)
Dosage Form and Route:	Immediate Release Sustained Release (b) (4)
Application Type/Number:	NDA 18644/S-047 NDA 20358/S-054 (b) (4)
Applicant:	Glasko Smith Kline (b) (4)

1 INTRODUCTION

WELLBUTRIN (bupropion hydrochloride) tablets was originally approved on December 30, 1995, for the treatment of major depressive disorder. WELLBUTRIN SR (bupropion hydrochloride) sustained release tablets was originally approved on October 4, 1996, for the treatment of major depressive disorder. (b) (4) [redacted] (b) (4) [redacted] On December 11, 2012, Glasko Smith Kline submitted a prior approval labeling supplement for WELLBUTRIN (bupropion hydrochloride) tablets and WELLBUTRIN SR (bupropion hydrochloride) sustained release tablets to be revised to conform with the Physician Labeling Rule (PLR) format.

This review is written in response to a request by the Division of Psychiatry Products (DPP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guides for WELLBUTRIN (bupropion hydrochloride) tablets, WELLBUTRIN SR (bupropion hydrochloride) sustained release tablets, (b) (4) [redacted]

2 MATERIAL REVIEWED

- Draft WELLBUTRIN (bupropion hydrochloride) tablets, WELLBUTRIN SR (bupropion hydrochloride) sustained release tablets, (b) (4) [redacted] Medication Guides received on December 11, 2012, and August 1, 2012, respectively and received by DMPP on May 15, 2013.
- Draft WELLBUTRIN (bupropion hydrochloride) tablets, WELLBUTRIN SR (bupropion hydrochloride) sustained release tablets, (b) (4) [redacted] Prescribing Information (PI) received on December 11, 2012, and August 1, 2012, respectively, revised throughout the review cycle, and received by DMPP on May 15, 2013.
- Approved APLENZIN (bupropion hydrobromide) extended release tablets dated August 14, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG documents using the Verdana font, size 11.

In our review of the Medication Guides we have:

- simplified wording and clarified concepts where possible
- ensured that the Medication Guides are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the Medication Guides meet the Regulations as specified in 21 CFR 208.20
- ensured that the Medication Guides meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the Medication Guides are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The Medication Guides are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the Medication Guides are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the Medication Guides.

Please let us know if you have any questions.

59 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

SHARON W WILLIAMS
05/23/2013

MELISSA I HULETT
05/23/2013

LASHAWN M GRIFFITHS
05/23/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 18-644/S-046/S-047
NDA 20-358/S-053/S-054

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 018644/S-047, NDA 20358/S-054

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Attention: Mary E. Martinson
Vice President, Neurosciences
Global Regulatory Affairs
5 Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Martinson:

We have received your Supplemental New Drug Applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA SUPPLEMENT NUMBERS:	NDA 018644/S-047, NDA 20358/S-054
PRODUCT NAME:	WELLBUTRIN (BUPROPION HYDROCHLORIDE) 75 MG AND 100 MG TABLETS WELLBUTRIN SR (BUPROPION HYDROCHLORIDE) SUSTAINED-RELEASE 100 MG, 150 MG, AND 200 MG TABLETS
DATE OF SUBMISSION:	December 11, 2012
DATE OF RECEIPT:	December 12, 2012

This supplemental application proposes the update the label to conform with the Physician Labeling Rule (PLR).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 10, 2013, in accordance with 21 CFR 314.101(a).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, email me at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

JULIETTE T TOURE
12/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 018644/S-046, NDA 20358/S-053

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

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Attention: Mary E. Martinson
Vice President, Neurosciences
Global Regulatory Affairs
5 Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Martinson:

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NDA SUPPLEMENT NUMBERS:	NDA 018644/S-046, NDA 20358/S-053
PRODUCT NAME:	WELLBUTRIN (BUPROPION HYDROCHLORIDE) 75 MG AND 100 MG TABLETS WELLBUTRIN SR (BUPROPION HYDROCHLORIDE) SUSTAINED-RELEASE 100 MG, 150 MG, AND 200 MG TABLETS
DATE OF SUBMISSION:	NOVEMBER 30, 2012
DATE OF RECEIPT:	NOVEMBER 30, 2012

This supplemental application proposes the following changes:

(b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 29, 2013, in accordance with 21 CFR 314.101(a).

Per a phone conversation between you and Juliette Touré of the Division of Psychiatry Products on December 18, 2012 and in response to an email received on December 18, 2012 proposing to resubmit this (b) (4)

(b) (4)

(b) (4)

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have questions, email Juliette Touré, PharmD, Senior Regulatory Project Manager, at Juliette.Toure@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director (acting)
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

MITCHELL V Mathis
12/19/2012

Toure, Juliette T

From: Toure, Juliette T
Sent: Friday, December 13, 2013 12:36 PM
To: jaisri.1.giridhar@gsk.com
Subject: Action requested: Wellbutrin IR and SR labeling
Attachments: FDA WSR label_13Dec2013.doc; FDA WIR label_13Dec2013.doc

Importance: High

Jaisri,

We've completed review of the Wellbutrin IR and SR labeling dated and received December 4, 2013. We would like to move forward with the action and plan make the following revisions:

Highlights

- Product title: Use all lower case letters for "tablets" and insert a comma after "tablets", i.e., "**WELLBUTRIN (bupropion hydrochloride) tablets, for oral use**".

Full Prescribing Information

- Remove line numbers throughout the FPI.

Medication Guide

- (b) (4) Remove bolding of all reportable conditions.

Let me know as soon as possible, no later than COB today if you have any concerns.

Thanks,
Juliette

Juliette Touré, PharmD, RAC
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

Commissioned Corps of the United States Public Health Service Mission: ***Protecting, promoting, and advancing the health and safety of the Nation.***

72 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

JULIETTE T TOURE
12/13/2013

Toure, Juliette T

From: Jaisri Giridhar <jaisri.1.giridhar@gsk.com>
Sent: Wednesday, December 18, 2013 3:32 PM
To: Toure, Juliette T
Subject: RE: Action requested: Wellbutrin IR and SR labeling

Hi Juliette,

Thank you for the email. We agree to (b) (4), as you have indicated.

We plan to submit a clean Word version of the PLR label supplement for Wellbutrin and Welbutrin SR to the respective NDAs, by Friday this week (December 20th) or earlier if possible.

Regards,
Jaisri

Jaisri Giridhar, PhD, DABT, RAC
Global Regulatory Affairs, Neurosciences
GlaxoSmithKline
R&D Building 5, 5 Moore Drive, RTP, NC 27709-3398
Tel:919-483-5984 (external) 703-5984 (internal)
Fax:919-483-5118
E-mail: jaisri.1.giridhar@gsk.com

From: Toure, Juliette T [mailto:Juliette.Toure@fda.hhs.gov]
Sent: Wednesday, December 18, 2013 11:32 AM
To: Jaisri Giridhar
Subject: RE: Action requested: Wellbutrin IR and SR labeling

Jaisri,

The division is ok with keeping the "T" capitalized; however, regarding the (b) (4). This placement is consistent with our current patient labeling practices and must be at the end because it applies to only a segment of the population who takes Wellbutrin. Please let me know by the end of the day of you concur.

Best,

Juliette

From: Jaisri Giridhar [mailto:jaisri.1.giridhar@gsk.com]
Sent: Monday, December 16, 2013 2:20 PM
To: Toure, Juliette T
Subject: RE: Action requested: Wellbutrin IR and SR labeling

Hi Juliette,

I am sending a response to the items that you had sent in the email Friday. Please see below.

1.FDA Comment:
Highlights

- Product title: Use all lower case letters for "tablets" and insert a comma after "tablets", i.e., "**WELLBUTRIN (bupropion hydrochloride) tablets, for oral use**".

GSK Response:
GSK wishes to keep the capital "T" as part of "WELLBUTRIN **T**ablets" and "WELLBUTRIN SR Sustained-Release **T**ablets" as this not only impacts the prescribing information for these products, but also affects the container labeling. As GSK's product names are presented with the initial letter of the finished dosage form capitalized on the container labeling, we prefer to keep the presentation of the product name consistent across the labeling for a product by keeping the initial letters of the finished dosage form capitalized on the prescribing information. According to the April 2013, draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Designs to Minimize Medication Errors*, Section IV.A., p. 9 suggests that capitalization of the finished dosage form on container labels and carton labeling is appropriate. The examples provided in the guidance highlight the acceptability of this approach noting as alternatives "Mydrug (drugozide) injection or Mydrug (drugozide) Injection" (where the "I" is capitalized). If there is another guidance that the Agency is following for this issue, GSK will greatly appreciate it if the Agency can share the information.

2. FDA Comment:
Full Prescribing Information

- Remove line numbers throughout the FPI.

GSK Response:
Thank you. GSK is agreeable to this change. We had intended to make this change and apologize for the oversight.

3. FDA Comment:
Medication Guide

- (b) (4). Remove bolding of all reportable conditions.

GSK Response:
GSK is agreeable t (b) (4) We are agreeable to the removal of bolding of all reportable conditions.

Thank you for your patience.

Regards,
Jaisri

Jaisri Giridhar, PhD, DABT, RAC
Global Regulatory Affairs, Neurosciences
GlaxoSmithKline

R&D Building 5, 5 Moore Drive, RTP, NC 27709-3398
Tel:919-483-5984 (external) 703-5984 (internal)
Fax:919-483-5118
E-mail: jaisri.1.giridhar@gsk.com

From: Toure, Juliette T [mailto:Juliette.Toure@fda.hhs.gov]
Sent: Friday, December 13, 2013 12:36 PM
To: Jaisri Giridhar
Subject: Action requested: Wellbutrin IR and SR labeling
Importance: High

Jaisri,

We've completed review of the Wellbutrin IR and SR labeling dated and received December 4, 2013. We would like to move forward with the action and plan make the following revisions:

Highlights

- Product title: Use all lower case letters for "tablets" and insert a comma after "tablets", i.e., "**WELLBUTRIN (bupropion hydrochloride) tablets, for oral use**".

Full Prescribing Information

- Remove line numbers throughout the FPI.

Medication Guide

- (b) (4). Remove bolding of all reportable conditions.

Let me know as soon as possible, no later than COB today if you have any concerns.

Thanks,
Juliette

Juliette Touré, PharmD, RAC
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

Commissioned Corps of the United States Public Health Service Mission: *Protecting, promoting, and advancing the health and safety of the Nation.*

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/s/

JULIETTE T TOURE
12/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: CDER/OND/ODE1/Division of Psychiatry Products Juliette Touré, PharmD – RPM, x65419 Robert Levin, MD – MTL x61110	
DATE 12/19/2012	IND NO.	NDA/BLA NO. 18644 (Wellbutrin) 20358 (Wellbutrin SR) (b) (4)	TYPE OF DOCUMENT Prior approval labeling supplement	DATE OF DOCUMENT 11/30/2012
NAME OF DRUG bupropion	NAME OF FIRM GSK (Wellbutrin, Wellbutrin SR) (b) (4)		CLASSIFICATION OF DRUG antidepressant	PDUFA Goal Date May 30, 2013
Requested Consult Completion Date: February 20, 2013	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☒ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): EDR Location: \\CDSESUB1\EVSPROD\NDA018644\018644.enx EDR Location: \\CDSESUB1\EVSPROD\NDA018644\0055	Materials to be reviewed: 1)References noted in the cover letter, particularly the new report submitted on August 10, 2012. 2) DEPI review, Steven Bird (11/20/12)

1. Please briefly describe the submission including drug's indication(s):
The sponsor has been monitoring a possible risk of congenital malformations and cardiovascular malformations among infants born to women exposed to buproprion during pregnancy. Bupropion is indicated for depression (MDD and Seasonal Affective Disorder, SAD) and smoking cessation (Zyban). They propose to update the language in the label in the pregnancy section (b) (4) They have cited their references in the cover letter. (b) (4) and would like to get the Agency's input.

2. Describe in detail the reason for your consult. Include specific questions:
We request your assistance in the review of the sponsor's referenced reports. You may have reviewed most of them. The newest report was submitted on August 10, 2012, accessible via the 1st link above. We request your input on the proposed labeling changes (b) (4) included in the submission.

3. Meeting dates:
To be determined.

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):
Reference ID: 3076070 (1/24/2012)
Reference ID: 2974009 (7/14/2011)

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PRINTED NAME or SIGNATURE OF REQUESTOR: Juliette Touré, PharmD	METHOD OF DELIVERY (Please check) ☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Final Study Report

Date:	November 20th, 2012
Reviewer(s):	Steven Bird, PharmD, MS, Regulatory Research Officer Division of Epidemiology I
Team Leader	Simone Pinheiro, Sc.D, M.Sc. Associate Director of Epidemiology & Team Leader Division of Epidemiology I
Division Director	Solomon Iyasu, MD, M.P.H. Director Division of Epidemiology I
Subject	Bupropion and Cardiac Birth Defects
Drug Name(s):	Bupropion
Application Type/Number:	NDA 18-644, 20-358, 20-711, 21-515, 22-108, 22-497
Submission Number:	398, 673
Applicant/sponsor:	GSK
OSE RCM #:	2012-2010

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

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EXECUTIVE SUMMARY

A recent study conducted by the Slone Epidemiology Center as Boston University at request of the sponsor suggested that taking bupropion during the first trimester of pregnancy can result in increased risk for ventricular septal defects (VSD) in the newborn. The Division of Psychiatric Products (DPP) in the Office of New Drugs (OND) consulted DEPI-1/OPE/OSE to review this study; results of the review are reported in this document.

Although this study has an excellent capture of cardiac birth defects, there are several main limitations. First, the limited number of exposed cases prevented adjustment for more than one or two covariates. Second, use of patient interview to obtain drug exposure after conception may lead mothers having a child with a birth defect to recall drug exposure to a better extent than mothers having children without birth defects (recall bias). Third, this study found a positive association between bupropion and VSD, while selective serotonin reuptake inhibitors (SSRI) were found to have positive associations with other cardiac defects. There is no explanation for why different antidepressant drugs would cause different cardiac defects. Fourth, it is possible that the small number of exposed cases leads to unstable point estimates and these results are chance findings. The null finding for use of bupropion in combination with other antidepressants has no plausible explanation. Sixth, a prior study by Alwan et al found a signal only with bupropion and left sided cardiac defects, while the current study found only a signal between bupropion and VSD. There is no explanation for these differences.

Overall, this was a well conducted study generating a safety signal for bupropion and VSD. However, the potential limitations prevent us from determining a causal association. Addition of the current study results to the product label will likely not add substantial content. It is possible that the risks associated with untreated depression, both for the mother and the infant, may outweigh any potential risk for birth defects. Inclusion of this information into the package insert does not provide additional clinically useful information beyond the classification of pregnancy category C.

We recommend the product label is updated to remove data on individual observational studies. Instead, we recommend that a summary statement is added to the label, indicating that observational studies have found conflicting results between maternal use of bupropion during pregnancy and cardiac defects in the newborn. This statement should reflect that a causal association could not be determined.

1 INTRODUCTION

A recent study conducted by the Slone Epidemiology Center at Boston University suggested that taking bupropion during pregnancy can result in ventricular septal defects (VSD) in the newborn.[1] The Division of Psychiatric Products (DPP) in the Office of New Drugs (OND) consulted DEPI-1/OPE/OSE to review this study; results of the review are reported in this document.

1.1 BACKGROUND

Bupropion hydrochloride was approved in the United States for treatment of major depressive disorder[2] and as an aid to smoking cessation treatment.[3] The bupropion hydrobromide formulation is also approved for the treatment of seasonal affective disorder in addition to major depressive disorder.[4] The product label indicates this product falls under pregnancy category C. This means that animal studies have shown an adverse effect on the fetus and there are no well done studies in humans; however the potential benefits may warrant use of the drug despite the potential risks.

Some women may in fact be prescribed bupropion during early pregnancy to help with smoking cessation because smoking has known teratogenic effects. Untreated depression has physical and mental effects on the mother and which could also potentially affect the fetus. To assess the potential for fetal birth defects with use of bupropion during pregnancy, GlaxoSmithKline established a pregnancy registry to capture women exposed to bupropion therapy during pregnancy. In the registry, among 675 women exposed to bupropion during pregnancy, 24 congenital malformations were observed, 9 of which were for congenital heart disease. The sponsor felt that a rate of 1% for cardiac birth defects, as seen in this registry, should be considered high.[5] Of note, this does compare to the incidence rate for congenital cardiac birth defects of approximately 1% as referenced by the Center for Disease Control.[6] The registry however was voluntary, did not collect data on a comparison group, and collected exposure information from patient interview after the outcome of a cardiac abnormality was known.

As a result of this registry, the manufacturer conducted a study[7] in the Ingenix Research Data Mart (RDM), a claims database with healthcare, medical, and prescriptions records. This study by Cole et al used billing codes for delivery to estimate the timing of the first trimester, and prescription dispensing dates were then used to determine antidepressant exposure. All reports of birth defects were verified through medical chart review. The study found similar risk for congenital malformations when bupropion was used during the first trimester compared to 1) other antidepressants used during the first trimester [Odds Ratio (OR) 0.95 and 95% Confidence Interval (95%CI): 0.62-1.45] and 2) when bupropion was used either during the 18 months prior to the first pregnancy or during the second two trimesters but not during the first trimester [OR 1.00 95%CI: 0.57-1.73]. A stratified analysis of cardiovascular congenital malformations also found no increased risk with bupropion compared to these same two reference groups [OR 0.97 95%CI: 0.52-1.80 and OR 1.07 95%CI: 0.52-1.80].

In 2008, a case-control study was conducted by Alwan et al[8] that matched cases of infants with major heart defects to controls. The study found a significant association between cardiac malformations in the infant and use of bupropion during pregnancy [OR

2.6 95%CI: 1.2-5.7]. This study did have some limitations, including 1) a small number of cases exposed to bupropion, 2) interview of mothers up to 24 months after delivery once outcome status was known (recall bias), 3) lack of information on dosage and indication for bupropion use, 4) a narrow range of defects, and 5) lack of an active comparator or repeated analysis with a control antidepressant. A review of this study was previously conducted by OSE/DEPI-1.[9]

To further investigate risk for congenital defects in children born to mothers that used bupropion during pregnancy, the sponsor conducted a study with Slone Epidemiology Center at Boston University. This study was reviewed in detail by OSE/DEPI-1 and that is the purpose of this review.

1.2 REGULATORY HISTORY

Bupropion hydrochloride was first approved for major depressive disorder in December of 1985 and later approved as an aid to smoking cessation therapy in May of 1997.[1,2] The hydrobromide formulation of bupropion was approved in April of 2008 for both major depressive disorder and seasonal affective disorder.[3] An update to the bupropion hydrochloride labels was made in July of 2006 to include a summary on an observation study evaluating cardiac defects with use of this drug (see summary of Cole et al above). (b) (4) The current labeling for bupropion and birth defects is below in the product labeling section.

1.3 PRODUCT LABELING

The bupropion hydrochloride and hydrobromide labels contain the following wording for cardiac birth defects:

"**Pregnancy Category C**

(b) (4)

1 Page Immediately Following Withheld - b(4) Draft Labeling

2 REVIEW METHODS AND MATERIALS

The following study materials were reviewed in detail by DEPI.

- Bupropion and Cardiac Birth Defects: a proposal from the Slone Epidemiology Center at Boston University. 15 July 2011.
  EDR Location: \\CDSESUB1\EVSPROD\NDA018644\018644.enx
- Louik C and (b) (4) First Trimester Exposure to Bupropion in Relation to the Risk of Cardiac Defects. A report by GlaxoSmithkline form Slone Epidemiology Center at Boston University. 11 July 2012.
  EDR Location: \\CDSESUB1\EVSPROD\NDA018644\018644.enx

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The following study evaluates the association between bupropion and cardiac birth defects. We will review the study objectives, study design, interpretation and analysis, and study conclusions. The review will then focus on the potential methodological limitations of this study and considerations for a labeling change.

3.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The objective of this study is to evaluate the association between bupropion and cardiac defects.

3.3 STUDY METHODS

3.3.1 Design & Setting

3.3.1.1 Study Type

- *Case-Control*

3.3.1.2 Population & Time Period

The Slone Epidemiology Birth Defect Study (BDS) was used to obtain cases and controls for this study. This study was initiated in 1976 and identifies congenital abnormalities at study centers in the following locations: areas surrounding Boston, Philadelphia, Toronto (through 2003), and San Diego (since 2000), as well as a portion of New York State (since 2004) and the entire state of Massachusetts (since 1998). In Philadelphia, Toronto, and San Diego, birth defects are identified by reviewing hospital admission and discharge records. Statewide birth defect registries are used to identify patients in New York and Massachusetts. The intent of the BDS is to capture major congenital defects. Minor defects are excluded and examples of minor defects include: accessory nipple, dislocatable hip, low set ears, skin tag, heart murmur, patient ductus arteriosus in premature infants, and patient foramen ovale in premature infants. The current study included cases from the BDS study between 1992 and 2010.

Information collected includes patient name, address telephone number, diagnostic information, and date of birth. As of 1992, the BDS began enrolling mothers of non-malformed infants; mothers are enrolled from participating hospitals and, since 1998, a population-based random sample of mothers were enrolled from Massachusetts.

Within six months of delivery, women are contacted for a 45-60 minute phone interview by a trained nurse unaware of the study hypotheses. Data is collected on demographics, reproductive and medical factors, health behaviors such as cigarette smoking, alcohol, and caffeine consumption, occupational exposure, and dietary intake. Information on medication exposure is also collected as described below (Section 3.3.2), as is information on history of other disease conditions.

3.3.1.3 Selection, Inclusion and Exclusion Criteria

Identification of mothers having infants with congenital defects and mothers of children without birth defects is described above (section 3.3.1.2). For inclusion into the current study, infants were required to have a congenital heart defect; primary defects of interest were ventricular septal defects (VSD), left-sided defects, coarctation of aorta, and hypoplastic left heart syndrome, although the study also looked at conotruncal and major arch abnormalities, atrial septal defects, right sided cardiac defects, and AV canal defects. Controls were selected as described above.

3.3.1.4 Protected Health Information (PHI) Requirements,

The study states the BDS study has been approved by the relevant institutional review boards and is compliant with all Health Information Portability and Accountability Act requirements.

3.3.2 Drug Exposure

During interview of the newborn's mother, information on medication exposure was collected, including prescriptions, over the counter drugs, vaccines, vitamins, and herbal products. Exposure was collected that occurred between two months prior to pregnancy until the completion of pregnancy. Dates of pregnancy trimesters were obtained through patient interview. Drug exposure during the first trimester of pregnancy was further broken down as follows:

1. Any exposure to bupropion in the first trimester
2. Exposure to bupropion alone among antidepressants
3. Exposure to bupropion in combination with another antidepressant
4. Exposure to an antidepressant other than bupropion
5. Exposure to an SSRI antidepressant with or without other antidepressants
6. Exposure to tricyclic antidepressants with or without other antidepressants
7. Exposure to an antidepressant other than bupropion, an SSRI, or a TCA

The reference for each group was women who had no exposure to any antidepressant at any time from 56 days prior to the last menstrual period (LMP) through the end of pregnancy. Women with exposure to an antidepressant outside of the first trimester (but not during the first trimester) were excluded (n=205) and women who reported a drug not classified as an antidepressant for the indication of depression were excluded (n=27).

3.3.3 Covariates

The following risk factors were assessed: maternal age, maternal race, maternal education, LMP year, study center, smoking history, alcohol consumption, family history of birth defects, family history of any cardiac defect in a first degree relative, pre-pregnant body mass index, gravidity, history of seizures, diabetes mellitus, hypertension, infertility, and periconceptional folic acid use.

3.3.4 Sample Size/Power

No information on sample size or power is provided.

3.3.5 Statistical Analyses

Logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95%CI). Covariates listed above were entered into the crude model individually, and risk factors changing the point estimate by ≥10% were retained in the final model.

3.4 STUDY RESULTS

The study identified 8,611 congenital cardiac defects; 2,734 were VSD, 1,233 had left-sided cardiac defects, 476 had coarctation of the aorta, 286 had hypoplastic left heart syndrome, and 3,184 with other cardiac defects.

Of the 8,611 controls, 4.3% were exposed to an antidepressant during the first trimester: 0.5% bupropion, 3.4% SSRIs, and 1.0% other antidepressants. Exposure to antidepressants in cases was as follows: 4.9% of VSD (0.9% bupropion), 5.0% of left-sided defects (0.2% bupropion), 6.2% of coarctation of aorta (0 bupropion), and 3.6% of hypoplastic left heart syndrome (0 bupropion).

The crude OR for the association between bupropion and VSD was 1.9 (95%CI: 1.1-3.2). Adjustment for study center and family history of birth defects reduced the OR to 1.6 (95%CI: 1.0-2.8). Stratified analysis found a significant adjusted OR for use of only bupropion [2.5 95%CI: 1.2-5.2] while use of bupropion with another antidepressant did not have a significant association [0.9 95%CI: 0.4-2.2] but had only six exposed cases. Bupropion did not have a significant association with any other subtype of cardiac defect.

The study also reported significant associations between other SSRIs (not including bupropion) and both left sided defects [OR 1.4 95%CI: 1.1-1.9] and coarctation of the aorta [OR 2.0 95%CI: 1.3-2.9]. For right sided cardiac defects, the study also reported: 1) a significant association between other antidepressants and conotrunal and major arch abnormalities [OR 1.5 95%CI: 1.2-2.0] and a non-significant effect with bupropion [OR 1.4 95%CI: 0.6-3.0], and 2) a significant association between other SSRIs and right sided cardiac defects [OR 1.6 95%CI: 1.2-2.1] but no association with bupropion [OR 1.0 95%CI: 0.4-2.9].

The investigators provide the association between each study covariate (covariates listed in section 3.3.3) and both exposure to bupropion (Table 1 of study report) and outcome of a cardiac defect (Table 2 of study report). Only the LMP year and a family history of cardiac defects were associated with both the exposure and outcome, confirming they are confounders for the association between bupropion and cardiac birth defects. Only 5 cases were reported to have been exposed to bupropion and a concomitant medication known to have teratogenic effects during the first trimester. Although the study planned a sub-analysis in women using the study drug for smoking cessation, only 17 women reported this indication and the sub-analysis was not performed.

3.5 STUDY CONCLUSIONS

The study reported increased risk for VSD with use of bupropion. The authors state there is no plausible explanation for why they did not also find risk for VSD when

bupropion was combined with other antidepressants. The authors also note differences in their results from the study by Alwan et al. First, the current study found a positive association for VSD with bupropion while Alwan et al did not. Second, Alwan et al found a positive association for left sided defects with bupropion, while the current study did not. There is no explanation for the different findings.

4 DISCUSSION

4.1 OVERALL SUMMARY

This case-control study identified 8,611 infants with congenital cardiac birth defects and matched 8,611 controls. Drug exposure and information on potential confounders was captured through patient interview within six months of delivery. This study assessed the association between exposure to bupropion during the first trimester of pregnancy and congenital cardiac birth defects. The reference comparator consisted of women who had no exposure to any antidepressant at any time from 56 days prior to the last menstrual period through the end of pregnancy.

The crude OR for the association between bupropion and ventricular septal defects (VSD) was 1.9 (95%CI: 1.1-3.2). Adjustment for study center and family history of birth defects reduced the OR to 1.6 (95%CI: 1.0-2.8). Stratified analysis found a significant adjusted OR for use of only bupropion [2.5 95%CI: 1.2-5.2] while use of bupropion with another antidepressant did not have a significant association [0.9 95%CI: 0.4-2.2] but had only six exposed cases. Bupropion did not have a significant association with any other subtype of cardiac defect.

Although this study has an excellent capture of cardiac birth defects, there are several main limitations. First, the limited number of exposed cases prevented adjustment for more than one or two covariates. Second, use of patient interview to obtain drug exposure after conception may lead mothers having a child with a birth defect to recall drug exposure to a better extent than mothers having children without birth defects (recall bias). Third, this study found a positive association between bupropion and VSD, while selective serotonin reuptake inhibitors (SSRI) were found to have positive associations with other cardiac defects. There is no explanation for why different antidepressant drugs would cause different cardiac defects. Fourth, it is possible that the small number of exposed cases leads to unstable point estimates and these results are chance findings. The null finding for use of bupropion in combination with other antidepressants has no plausible explanation. Sixth, a prior study by Alwan et al found a signal only with bupropion and left sided cardiac defects, while the current study found only a signal between bupropion and VSD. There is no explanation for these differences.

4.2 POINT BY POINT DISCUSSION COMMENTS

Design

1. This study uses a case-control design. Given the rare occurrence of cardiac defects and the use of patient interview to collect additional information, this design choice was appropriate.

Outcome

2. This study recruited cases systematically through several US hospitals and statewide registries. This was an appropriate source of data on birth defect cases.

Exposure

3. Exposure was obtained through interview during the six months after conception. Although this is better than the exposure definition from the study by Alwan et al (which allowed a maximum timeframe of two years for the patient interview), this ascertainment is still subject to a recall bias. Mothers giving birth to a child with a birth defect may be more likely to remember a specific drug exposure.

Comparator

4. The comparator consists of women who did not use antidepressants from 56 days prior to the LMP to the end of pregnancy. The analysis is then repeated with control antidepressants. Because the study analysis was repeated with control antidepressants, this is an appropriate comparison group.
5. Controls are described as a population based sample, where controls are selected from the same hospitals as the cases. However, no further information on control selection is provided. Through observation of the results, we can see there was a 1:1 selection.

Covariates

6. This study assessed many of the major potential confounders for this association and confirmed only two covariates to be true confounders. However, the small number of events made it impossible to adjust for more than one or two covariates in each analysis. There is potential for residual confounding.

Sample Size

7. Although no a priori power calculation is provided, this study has a large number of cases, especially for such a rare outcome. The confidence interval width can be used to assess power for each individual analysis. Although power may be limited for some subanalyses, this is the ideal sample for this type of analysis.

Statistical Analysis

8. Use of logistic regression was appropriate.

Results

9. The point estimates vary by cardiac defect. Bupropion was found to have a positive association for VSD, while other SSRIs were found to have significant associations with other cardiac defects. There is no explanation for why different SSRI drugs would cause different cardiac defects. It is possible that the small number of exposed cases leads to unstable point estimates and these results are chance findings.

Conclusions

10. The study authors provide a balanced discussion on the signal for VSD with bupropion and the potential for bias based on the potential study limitations.

5 CONCLUSION

Overall, this was a well conducted study generating a safety signal for bupropion and VSD. However, the potential limitations prevent us from determining a causal association. Addition of the current study results to the product label will likely not add substantial content. It is possible that the risks associated with untreated depression, both for the mother and the infant, may outweigh any potential risk for birth defects. Inclusion of this information into the package insert does not provide additional clinically useful information beyond the classification of pregnancy category C.

6 RECOMMENDATIONS

We recommend the product label is updated to remove data on individual observational studies. Instead, we recommend a summary statement is added to the label, indicating that observational studies have found conflicting results between maternal use of bupropion during pregnancy and cardiac defects in the newborn. This statement should reflect that a causal association could not be determined.

7 REFERENCES

[1] Bupropion and Cardiac Birth Defects: a proposal from the Slone Epidemiology Center at Boston University. 15 July 2011. EDR Location: \\CDSESUB1\EVSPROD\NDA018644\018644.enx

[2] Bupropion [package insert]. Irvine, CA: Anchen Pharmaceuticals, Inc.; 2006.

[3] Zyban [package insert]. Greenville, NC: GlaxoSmithKline; 2012

[4] Aplenzin [package insert]. Bridgewater, NJ: Sanofi-Aventis LLC; 2012.

[5] Louik C and (b) (4) First Trimester Exposure to Bupropion in Relation to the Risk of Cardiac Defects. A report by GlaxoSmithkline form Slone Epidemiology Center at Boston University. 11 July 2012. EDR Location: \\CDSESUB1\EVSPROD\NDA018644\018644.enx

[6] Congenital Heart Defects: Data & Statistics. Center for Disease Control. Atlanta, GA. Updated 12 September 2011. Available at http://www.cdc.gov/ncbddd/heartdefects/data html#ref. Accessed on 10 September 2012.

[7] Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiol Drug Saf* 2007;16:474-84.

[8] Alwan S, Reefhuis J, Botto LD, et al. Maternal use of bupropion and risk for congenital heart defects. *Am J Obstet Gynecol* 2010;203(1):52.e1-6.

[9] Shih D. Review of study report "Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations – Additional Analysis: Final Brief Report." FDA Review. 29 December 2011. Reference ID: 3064833

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEVEN BIRD
11/20/2012

SIMONE P PINHEIRO
11/20/2012

SOLOMON IYASU
11/20/2012

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIETTE T TOURE
12/19/2012

MITCHELL V Mathis
12/20/2012

Toure, Juliette T

From: Toure, Juliette T
Sent: Thursday, November 21, 2013 1:20 PM
To: jaisri.1.giridhar@gsk.com
Subject: Wellbutrin IR and SR PLR Conversion - label edits
Attachments: WIR_FDA edits based on GSK draft from 24Oct2013.doc; WSR FDA edits based on GSK draft from 24Oct2013.doc

Jaisir,

We have reviewed your PLR conversion submissions, dated 24 October 2013. In the attached documents – we have made a couple minor edits that should be incorporated into your next label submission. Please let me know when you will be able to send the updated labels with these changes as well as the formatting changes noted in my email from November 13, 2013.

Thanks,
Juliette

Juliette Touré, PharmD, RAC
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

73 Pages Immediately Following Withheld - b(4) Draft Labeling

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIETTE T TOURE
11/21/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**WELLBUTRIN (bupropion hydrochloride) tablets, for oral use**
Applicant	GlaxoSmithKline
Application/Supplement Number	NDA 18644/S-047
Type of Application	PLR Conversion
Indication(s)	Treatment of major depressive disorder
Established Pharmacologic Class[1]	Aminoketone antidepressant
Office/Division	ODEI/DPP
Division Project Manager	Juliette Toure
Date FDA Received Application	December 12, 2012
Goal Date	June 12, 2013
Date PI Received by SEALD	October 29, 2013
SEALD Review Date	October 31, 2013
SEALD Labeling Reviewer	Debra Beitzell
SEALD Division Director	Laurie Burke

[1] The product title or established pharmacologic class that appears in draft agreed-upon prescribing information (PI).

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *DPP to grant waiver of 1/2 page HL limit in approval letter.*

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

YES 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment: *Insert month/year of supplement approval.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

YES 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> *"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."*

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Reference to FDA-approved patient labeling consistent with the recommendations in the new Patient Counseling Information guidance.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEBRA C BEITZELL
10/31/2013

ERIC R BRODSKY
10/31/2013
I agree. Eric Brodsky, SEALD labeling team leader, signing for Laurie Burke, SEALD director.

Toure, Juliette T

From: Toure, Juliette T
Sent: Thursday, October 17, 2013 10:10 AM
To: 'jaisri.1.giridhar@gsk.com'
Cc: Mary Martinson (mary.e.martinson@gsk.com)
Subject: Wellbutrin NDA 18644 and NDA 20358 PLR label
Attachments: FDA label_NDA 18644_WIR_17Oct2013.doc

Jaisiri,

I received notification that you are now the regulatory affairs point of contact for Wellbutrin NDA 18644 and Wellbutrin SR NDA 20358. I've cc'd Mary since have been working together on the PLR conversion of these labels.

You'll find attached our revisions and comments regarding some of your proposed edits from GSK's last labeling amendment dated Sep 13, 2013. I hope to come to agreement with you on the label with you shortly. Please let me know if you agree with the attached label by **NLT Thursday COB, October 24**. If you agree with the label, please also update the Wellbutrin SR label accordingly and resubmit the amended label to the NDA.

Kind regards,
Juliette

Juliette Touré, PharmD, RAC
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

Commissioned Corps of the United States Public Health Service Mission: ***Protecting, promoting, and advancing the health and safety of the Nation.***

39 Pages Immediately Following Withheld - b(4) Draft Labeling

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIETTE T TOURE
10/17/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Friday, August 30, 2013 4:08 PM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: FDA Wellbutrin draft label for sponsor_28Aug2013.doc
Attachments: FDA Wellbutrin draft label for sponsor_28Aug2013.doc

Dear Mary,

In reference to the label dated and received June 21, 2013, we have reviewed your edits and provided explanations via comments in the attached label.

Please let me know if you agree with the changes in the this label by NLT one week from today. Also, please resubmit and update the Wellbutrin SR label accordingly.

Thanks,
Juliette

Juliette Touré, PharmD, RAC
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

Commissioned Corps of the United States Public Health Service Mission: ***Protecting, promoting, and advancing the health and safety of the Nation.***

36 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

JULIETTE T TOURE
09/03/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Thursday, June 13, 2013 11:16 AM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: NDA 18644 S-047 and Wellbutrin SR NDA 20358 S-054 PLR conversions
Attachments: FDA label_NDA18644 Wellbutrin IR based on 14Dec2012 draft.doc; DNP - Aubagio (teriflunomide) - format review of the prescribing information.pdf; DNP - Oxtellar XR (oxcarbazepine) - format review of the prescribing information.pdf; DNP - Fycompa (perampanel) - format review of the prescribing information.pdf

Hi Mary,

We have reviewed your proposed label for the PLR conversion of Wellbutrin and Wellbutrin SR, NDAs 18644 and 20358, respectively. We have made significant changes throughout the label for Wellbutrin (IR) and have included comments to either explain some of the change or request additional edits.

Please review these changes and resubmit updated labels for both Wellbutrin and Wellbutrin SR, using this draft. If you don't agree with the changes please provide the justification. Let me know if you have any questions.

Finally, please review the attached format reviews done for the attached labels. You will need to ensure that when you resubmit the Wellbutrin labels, the formatting must meet the requirements laid out in the attached format reviews, to be in conformance with PLR format.

We request that you resubmit these labels as soon as possible, NLT 1 week from today.

Thanks,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

27 Pages Immediately Following Withheld - b(4) Draft Labeling

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**TRADENAME (teriflunomide) tablets, for oral administration**
Applicant	Sanofi-Aventis U.S. LLC
Application/Supplement Number	NDA 202992
Type of Application	Original NDA
Indication	Treatment of patients with relapsing forms of multiple sclerosis
Established Pharmacologic Class[1]	None stated
Office/Division	Office of Drug Evaluation I/Division of Neurology Products
Division Project Manager	Hamet Touré
Receipt Date	August 12th, 2011
PDUFA Goal Date	September 12th, 2012
SEALD Review Date	August 28th, 2012
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Labeling Team Leader	Eric Brodsky
SEALD Division Director	Laurie Burke

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The summarized statement under the heading "Use in Specific Populations" does not reference the section (s) or subsection (s) of the Full PrescribingInformation (FPI).*

We recommend that you delete the optional section heading entitled "Use in Specific Population" because the information provided under this section is the same as the information provided under the required section heading entitled "Contraindication".

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required

Selected Requirements of Prescribing Information (SRPI) Revised

• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment: *Recommend that "for oral administration" be changed to "for oral use."*

Initial U.S. Approval

NO 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *The 4-digit year is missing from the placeholder*

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

NO 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and

other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *The subject of the Warning (e.g., WARNING: HEPATOTOXICITY AND RISK OF TERATOGENICITY) is missing.*

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

NO 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment: *The current length of the Boxed Warning in the HL is 22 lines. It is very important to reduce the length to 20 lines or less.*

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

N/A 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *The name of the established pharmacologic class is missing from the Indications and Usage statement in the HL. Elist does not list an EPC for this product. When an EPC is available, please include it.*

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment: *Recommend that the words "film-coated" is deleted because identifying characteristics of the dosage form should not be included in Highlights. Only include this information in the FPI.*

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

NO 24. Each contraindication is bulleted when there is more than one contraindication.
Comment: *Bullets for the two contraindication listed are missing.*

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".
Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment: *The bolded revision date is missing from the placeholder.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.
Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

For section 5, "Warning and Precautions", the subheadings for 5.1, 5.2, and 5.12 in the TOC do not match the subheadings in the FPI.

For section 7 "Drug Interactions" we recommend using subheadings for the different drug interactions described.

For section 8 ""Use in Specific Populations" the subheadings for 8.2, 8.6 and 8.7 in the TOC do not match the subheadings in the FPI. In addition, subheading 8.6 in the FPI is missing from the TOC.

For section 17 "Patient Counseling Information" the subheadings 17.2, 17.3, 17.4, 17.5 and 17.6 in the TOC do not match the subheadings in the FPI. in addition, subheadings 17.7, 17.8, 17.9 and 17.10 included in the FPI is missing from the TOC.

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment: *The same title of the Boxed Warning that appears in the HL and FPI is missing from the beginning of the TOC in UPPER-CASE letters and bold type.*

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment: *Recommend that this heading be justified to the left rather than centered.*

NO 37. All section and subsection headings and numbers must be **bolded**.

Comment: *For Section 4 "Contraindications" subheading 4.1 is missing from the FPI*

For section 5 "Warnings and Precautions" subheading 5.7 number is not bolded

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Selected Requirements of Prescribing Information (SRPI) Revised

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *The presentation for cross-references in the FPI for the following sections and subsections need to be changed to the preferred presentation as follows:*

For subsection 5.2: Change [see CONTRAINDICATIONS (4.2)] to [see Contraindications (4.2)]
For section 7: Include cross reference to the more detailed information in section 12.
For subsection 8.8: Change (see WARNINGS (5.7, 5.8) to [see Warnings and Precautions (5.7, 5.8)]

For section 10: Change *[see* WARNINGS AND PRECAUTIONS (5.3) *and Clinical Pharmacology* (12.3)] to *[see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*]

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

NO 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment: *Subject of the warning is not identified in the heading.*

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment: *The verbatim statement needs to be moved up from its current position in the label so that it precedes the presentation of adverse reactions in the "Clinical Trials Experience" subsection of Adverse Reactions.*

47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

N/A

"*The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."*

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Patient Counseling Information

NO

48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment: *Change from "See Medication Guide" to "See FDA-approved patient labeling (Medication Guide)" without the quotation marks*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABIMBOLA O ADEBOWALE
08/29/2012

ERIC R BRODSKY
08/29/2012
I agree

LAURIE B BURKE
08/30/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**FYCOMPA (perampanel) tablets for oral use**
Applicant	Eisai
Application/Supplement Number	NDA 202834 S1
Type of Application	Original NDA
Indication	"Adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older"
Established Pharmacologic Class[1]	non-competitive AMPA glutamate receptor antagonist
Office/Division	ODEI/DNP
Division Project Manager	Stephanie Parncutt
Date FDA Received Application	December 22, 2011
Goal Date	October 22, 2012
Date PI Received by SEALD	October 22, 2012
SEALD Review Date	October 22, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Contraindications header is shifted to the right.*

YES 4. White space must be present before each major heading in HL.

Comment:

NO 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *Neurologic Effects in Warnings and Precaution, Boxed Warning.*

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

YES 12. All text must be **bolded**.

Comment:

YES 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

YES 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

YES 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

YES 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

YES 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

NO 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES 42. All text is **bolded**.

Comment:

YES 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

YES 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC R BRODSKY
10/22/2012

LAURIE B BURKE
10/22/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**OXTELLAR XR (oxcarbazepine) extended-release tablets, for oral use**
Applicant	Supernus
Application/Supplement Number	NDA 202810-S-1
Type of Application	Original NDA
Indication	Adjunctive therapy of partial seizures in adults and children 6 to 17 years old
Established Pharmacologic Class[1]	Antiepileptic drug (AED)
Office/Division	ODEI/DNP
Division Project Manager	Stephanie Parncutt
Date FDA Received Application	December 19, 2011
Goal Date	October 19, 2012
Date PI Received by SEALD	October 18, 2012
SEALD Review Date	October 18, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Horizontal line should be extended for the headings in HL.*

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*****

Selected Requirements of Prescribing Information

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *The proprietary name should be in UPPER-CASE.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." in *italics* and centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

NO 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment: *Move this statement to end of TOC.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)

12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *One cross-reference in Section 8.4 and one in Section 17 are not correct.*

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ERIC R BRODSKY
10/18/2012

LAURIE B BURKE
10/18/2012

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/s/

JULIETTE T TOURE
06/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER/OND/ODE1/Division of Psychiatry Products
Juliette Touré, PharmD – RPM, x65419
Robert Levin, MD – MTL x61110

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
5/13/2013		18644/S-047 (Wellbutrin) 20358/S-054 (Wellbutrin SR) (b) (4)	(PLEASE CHECK OFF BELOW) Prior Approval Supplement for PLR Conversions

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 1 Week before the wrap up mtg)
Bupropion	Standard	Antidepressant	5/31/2013

NAME OF FIRM:
GSK (Wellbutrin, Wellbutrin SR)
(b) (4)

PDUFA Date: 6/12/2013 (WIR, WSR), (b) (4)

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☒ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission: \\CDSESUB5\EVSPROD\NDA018644\018644.enx
\\CDSESUB5\EVSPROD\NDA020358\020358.enx
(b) (4)

Eroom link to draft labels (please check with me on which version/document to review – we are starting with Wellbutrin IR): http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_b8e68

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings:

- May 13, 2013, 2-3pm EST, Rm 4201 in Bldg 22 – The objective of the meeting is discuss the label and finalize SCPI for you by May 17.
- June 4, 2013, 9-10am EST, Rm 3201 in Bldg 22 – The objective of the meeting is to discuss the label and finalize the label for label negotiations and if needed, discuss OPDP and PLT edits to the PI and MG.

I will invite you as optional participants to these meetings and any future meetings (as needed).

SIGNATURE OF REQUESTER Juliette Touré, PharmD, Rm 4249, Bldg 22

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

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/s/

JULIETTE T TOURE
05/13/2013

MITCHELL V Mathis
05/13/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER/OND/ODE1/Division of Psychiatry Products
Juliette Touré, PharmD – RPM, x65419
Robert Levin, MD – MTL x61110

REQUEST DATE:
5/13/2013

NDA/BLA NO.:
18644/S-047 (Wellbutrin)
20358/S-054 (Wellbutrin SR)
(b) (4)

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

Prior Approval Supplement for PLR Conversions

NAME OF DRUG:
Bupropion

PRIORITY CONSIDERATION:
Standard

CLASSIFICATION OF DRUG:
Antidepressant

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)

5/31/2013

SPONSOR:
GSK (Wellbutrin, Wellbutrin SR)
(b) (4)

PDUFA Date: 6/12/2013

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
☐ PATIENT PACKAGE INSERT (PPI)
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ MANUFACTURING (CMC) SUPPLEMENT
☒ PLR CONVERSION

REASON FOR LABELING CONSULT
☐ INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB5\EVSPROD\NDA018644\018644.enx
\\CDSESUB5\EVSPROD\NDA020358\020358.enx
(b) (4)
Eroom link to draft labels (please check with me on which version/document to review – we are starting with Wellbutrin IR): http://eroom.fda.gov/eRoom/CDER/CDER-NPC/0_b8e68

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings:

- May 13, 2013, 2-3pm EST, Rm 4201 in Bldg 22 – The objective of the meeting is discuss the label and finalize SCPI for you by May 17.
- June 4, 2013, 9-10am EST, Rm 3201 in Bldg 22 – The objective of the meeting is to discuss the label and finalize the label for label negotiations and if needed, discuss OPDP and PLT edits to the PI and MG.

I will invite you as optional participants to these meetings and any future meetings (as needed).

SIGNATURE OF REQUESTER: Juliette Touré, PharmD, Rm 4249, Bldg 22

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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/s/

JULIETTE T TOURE
05/13/2013

MITCHELL V Mathis
05/13/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Monday, May 13, 2013 4:37 PM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: Food effect study for Wellbutrin IR

Hi Mary,

Was a food effect study conducted for Wellbutrin IR? If so, can you please submit the report?

Thanks,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

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/s/

JULIETTE T TOURE
05/13/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Friday, April 12, 2013 7:50 AM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: Wellbutrin PLR conversion - IR

Hi Mary,

We are reviewing the Wellbutrin PLR conversions and would like to request the bupropion hepatic impairment and renal impairment study reports and summaries.

Thank you,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

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/s/

JULIETTE T TOURE
04/12/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Thursday, April 04, 2013 2:39 PM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: Wellbutrin rabbit study data - IR Request

Hi Mary,

The original submission of NDA 18-644 for Wellbutrin Tablets (received 12/23/1981) contained reports for 2 embryo-fetal development studies conducted in rabbits. We would like to re-review those studies in order to update labeling. We ask that you re-submit those reports, as soon as possible, **preferably by April 16th**.

Thank you,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

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/s/

JULIETTE T TOURE
04/04/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Thursday, March 21, 2013 12:03 PM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: NDAs 18644/S-047, 20358/S-054 PLR conversion

Mary,

In reference to your submission received on March 13, 2013, we have the following additional comments/requests:

[1] We would like to clarify that the footnote c to the sample Table in our email request dated March 1 indicates that "Difference from Placebo" is the difference between drug response and placebo response, where drug response refers to the change from baseline to the endpoint visit. We believe that this should be consistent with the primary efficacy variable in the study reports. If so, please fill in the table as provided below.

The efficacy summary table will mark doses that were shown superior to placebo in each trial. Instead of reporting p-values, unadjusted 2-sided 95% CI will be included for effective doses only. If possible, please provide the missing information as indicated in the table below.

Table 1: Summary of Efficacy Results for Bupropion

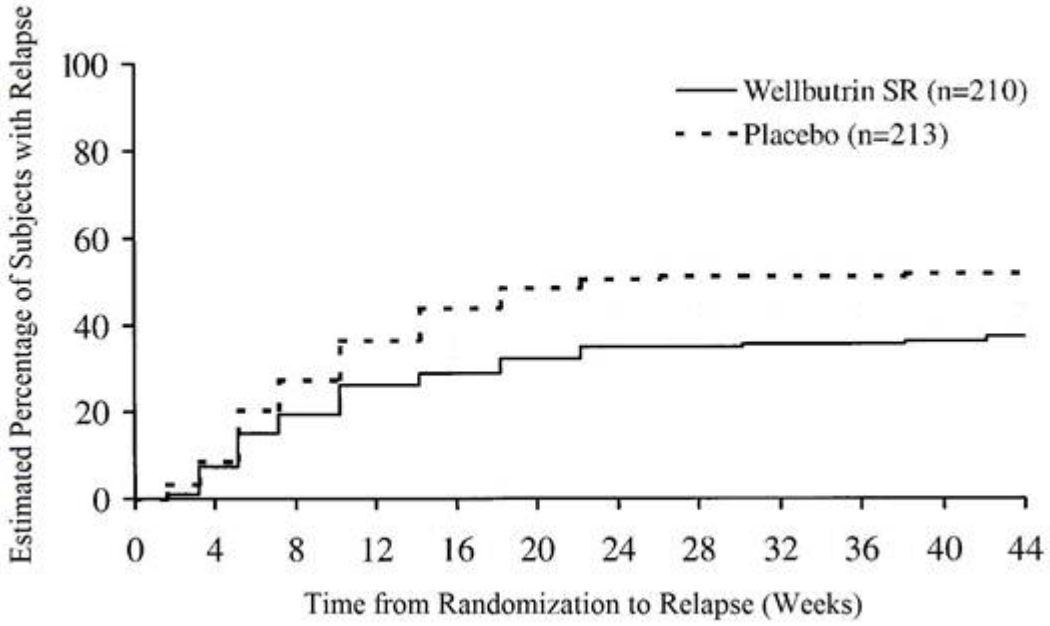
Study No.	Primary Efficacy Measure:	Placebo	Bupropion (300 mg/day)	Bupropion (450 mg/day)	Bupropion (300 – 600 mg/day)
1.	HDRS	n=27	--	--	n=48
	Mean Baseline (SD)	29.3 (7.0)	--	--	28.5 (5.1)
	LS Mean Change from Baseline (SE)	? (?)	--	--	? (?)
	Difference from Placebo[a] (95% CI)	--	--	--	?* (?, ?)
2.	HDRS	n=39	n=36	n=34	--
	Baseline	32.9 (5.4)	32.4 (5.9)	34.8 (4.6)	--
	LS Mean Change from Baseline (SE)	? (?)	? (?)	? (?)	--
	Difference from Placebo[a] (95% CI)	--	?	?* (?, ?)	--
3.	HDRS	n=106	n=110	--	--
	Baseline	27.02 (3.48)	26.54 (4.24)	--	--
	LS Mean Change from Baseline (SE)	--	? (?)	--	--
	Difference from Placebo[a] (95% CI)	--	?* (?, ?)	--	--

LS mean: least-squares mean; SD: standard deviation; SE: standard error.
* Doses that were shown to be statistically significantly superior to placebo.
a) LS mean change from baseline in drug group minus the placebo group, where unadjusted 2-sided 95% confidence interval is included for dose that was shown to be statistically significantly

superior to placebo.

[2] With regard to the time to relapse plot for the maintenance study, (b) (4) in Section 14 of the labeling. As a result, (b) (4). We have also revised the axis labels to enhance clarification as shown below. If you would like to re-draw the plot to incorporate these changes, please do so.

Figure 2. Time to Relapse/Recurrence of Depression



Thank you,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

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/s/

JULIETTE T TOURE
03/21/2013

Toure, Juliette T

From: Toure, Juliette T
Sent: Friday, March 01, 2013 7:51 AM
To: Mary Martinson (mary.e.martinson@gsk.com)
Subject: NDA 18644 / S-047 and NDA 20358 / S-054 - Wellbutrin PLR conversion labeling supplements

Hi Mary,

In reference to the prior approval labeling supplements received December 12, 2012 to convert the Wellbutrin and Wellbutrin SR labels to PLR format, we request that you provide the following:

[1] For each short-term efficacy study included in Section 14, please provide primary efficacy results using the following table as a sample.

Table 8: xxxxxx

Study No.	Primary Endpoint	Placebo	Bupropion (300 mg/day)	Bupropion (450 mg/day)	Bupropion (300 – 600 mg/day)
1	HDRS Baseline Score (SD[a])	xxx (xxx)	xxx (xxx)	xxx (xxx)	xxx (xxx)
	Difference from Placebo (95% CI[c])		xxx[b] (xxx, xxx)	xxx (xxx, xxx)	XXX
2					

[a] Standard deviation;
[b] Adjusted p-value < 0.05 (i.e., doses shown superior to placebo);
[c] Difference between least squares means at final evaluation, calculated as drug response minus placebo response; unadjusted 95% confidence intervals are included for doses that were shown superior to placebo.

[2] For each maintenance study included in Section 14, please provide Kaplan-Meier curves, where the vertical axes denotes the estimated proportion of patients with relapse.

Thank you,
Juliette

Juliette Touré, PharmD
CDR, United States Public Health Service
Senior Regulatory Project Manager
U.S. Food and Drug Administration
Division of Psychiatry Products
(301) 796-5419

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/s/

JULIETTE T TOURE
03/01/2013