

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

Warnings and Precautions, Angle-Closure Glaucoma (5.7) 07/2014

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, 5.8)

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)
- Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and $\geq 1\%$ 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*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 General Instructions for Use
- 2.2 Dose Adjustment in Patients with Hepatic Impairment
- 2.3 Dose Adjustment in Patients with Renal Impairment
- 2.4 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant
- 2.5 Use of WELLBUTRIN with Reversible MAOIs Such as Linezolid or Methylene Blue

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
- 5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

- 5.3 Seizure
- 5.4 Hypertension
- 5.5 Activation of Mania/Hypomania
- 5.6 Psychosis and Other Neuropsychiatric Reactions
- 5.7 Angle-Closure Glaucoma
- 5.8 Hypersensitivity Reactions
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Trials Experience
 - 6.2 Postmarketing Experience
- 7 DRUG INTERACTIONS
 - 7.1 Potential for Other Drugs to Affect WELLBUTRIN
 - 7.2 Potential for WELLBUTRIN to Affect Other Drugs
 - 7.3 Drugs that Lower Seizure Threshold
 - 7.4 Dopaminergic Drugs (Levodopa and Amantadine)
 - 7.5 Use with Alcohol
 - 7.6 MAO Inhibitors
 - 7.7 Drug-Laboratory Test Interactions
- 8 USE IN SPECIFIC POPULATIONS
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers

- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment
- 9 **DRUG ABUSE AND DEPENDENCE**
 - 9.1 Controlled Substance
 - 9.2 Abuse
- 10 **OVERDOSAGE**
 - 10.1 Human Overdose Experience
 - 10.2 Overdosage Management

- 11 **DESCRIPTION**
 - 12 **CLINICAL PHARMACOLOGY**
 - 12.1 Mechanism of Action
 - 12.3 Pharmacokinetics
 - 13 **NONCLINICAL TOXICOLOGY**
 - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 - 14 **CLINICAL STUDIES**
 - 16 **HOW SUPPLIED/STORAGE AND HANDLING**
 - 17 **PATIENT COUNSELING INFORMATION**
- *Sections or subsections omitted from the full prescribing information are not listed.

1 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)*].

33 **2 DOSAGE AND ADMINISTRATION**

34 **2.1 General Instructions for Use**

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

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

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

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

52 **2.2 Dose Adjustment in Patients with Hepatic Impairment**

53 In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the
54 maximum dose of WELLBUTRIN is 75 mg per day. In patients with mild hepatic impairment
55 (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [*see Use in*
56 *Specific Populations (8.7), Clinical Pharmacology (12.3)*].

57 **2.3 Dose Adjustment in Patients with Renal Impairment**

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

61 **2.4 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI)**
62 **Antidepressant**

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

67 **2.5 Use of WELLBUTRIN with Reversible MAOIs Such as Linezolid or**
68 **Methylene Blue**

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

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

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

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

87 **3 DOSAGE FORMS AND STRENGTHS**

- 88 • 75 mg – yellow-gold, round, biconvex tablets printed with “WELLBUTRIN 75”.
- 89 • 100 mg – red, round, biconvex tablets printed with “WELLBUTRIN 100”.

90 **4 CONTRAINDICATIONS**

- 91 • WELLBUTRIN is contraindicated in patients with a seizure disorder.
- 92 • WELLBUTRIN is contraindicated in patients with a current or prior diagnosis of bulimia or
93 anorexia nervosa as a higher incidence of seizures was observed in such patients treated with
94 WELLBUTRIN [see *Warnings and Precautions (5.3)*].
- 95 • WELLBUTRIN is contraindicated in patients undergoing abrupt discontinuation of alcohol,
96 benzodiazepines, barbiturates, and antiepileptic drugs [see *Warnings and Precautions (5.3),*
97 *Drug Interactions (7.3)*].
- 98 • The use of MAOIs (intended to treat psychiatric disorders) concomitantly with
99 WELLBUTRIN or within 14 days of discontinuing treatment with WELLBUTRIN is
100 contraindicated. There is an increased risk of hypertensive reactions when WELLBUTRIN is
101 used concomitantly with MAOIs. The use of WELLBUTRIN within 14 days of
102 discontinuing treatment with an MAOI is also contraindicated. Starting WELLBUTRIN in a
103 patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is
104 contraindicated [see *Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.4),*
105 *Drug Interactions (7.6)*].
- 106 • WELLBUTRIN is contraindicated in patients with known hypersensitivity to bupropion or
107 other ingredients of WELLBUTRIN. Anaphylactoid/anaphylactic reactions and Stevens-
108 Johnson syndrome have been reported [see *Warnings and Precautions (5.8)*].

109 **5 WARNINGS AND PRECAUTIONS**

110 **5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young**
111 **Adults**

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

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

126 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
127 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24
128 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of
129 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of
130 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000
131 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency
132 toward an increase in the younger subjects for almost all drugs studied. There were differences in
133 absolute risk of suicidality across the different indications, with the highest incidence in MDD.
134 The risk differences (drug vs. placebo), however, were relatively stable within age strata and
135 across indications. These risk differences (drug-placebo difference in the number of cases of
136 suicidality per 1,000 subjects treated) are provided in Table 1.

137
138 **Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled**
139 **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

140

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

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

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

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

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

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

170 **5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation** 171 **Treatment**

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

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

183 **5.3 Seizure**

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

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

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

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

206 **5.4 Hypertension**

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

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

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

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

229 **5.5 Activation of Mania/Hypomania**

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

236 **5.6 Psychosis and Other Neuropsychiatric Reactions**

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

242 **5.7 Angle-Closure Glaucoma**

243 The pupillary dilation that occurs following use of many antidepressant drugs including
244 WELLBUTRIN may trigger an angle-closure attack in a patient with anatomically narrow angles
245 who does not have a patent iridectomy.

246 **5.8 Hypersensitivity Reactions**

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

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

256 **6 ADVERSE REACTIONS**

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

- 259 • Suicidal thoughts and behaviors in adolescents and young adults [see Boxed Warning,
- 260 Warnings and Precautions (5.1)]
- 261 • Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [see Boxed
- 262 Warning, Warnings and Precautions (5.2)]
- 263 • Seizure [see Warnings and Precautions (5.3)]
- 264 • Hypertension [see Warnings and Precautions (5.4)]
- 265 • Activation of mania or hypomania [see Warnings and Precautions (5.5)]
- 266 • Psychosis and other neuropsychiatric reactions [see Warnings and Precautions (5.6)]
- 267 • Angle-closure glaucoma [see Warnings and Precautions (5.7)]
- 268 • Hypersensitivity reactions [see Warnings and Precautions (5.8)]

269 **6.1 Clinical Trials Experience**

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

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

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

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

290 **Table 2. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater**
 291 **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

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Other Adverse Reactions Observed During the Clinical Development of

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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.

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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.

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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.

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Dermatologic: Infrequent was alopecia.

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Endocrine: Infrequent was gynecomastia; rare was glycosuria.

308

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

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

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

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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.

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

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322

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

323

324 *Special Senses:* Infrequent was visual disturbance; rare was diplopia.
325 *Nonspecific:* Frequent were flu-like symptoms; infrequent was nonspecific pain; rare
326 was overdose.

327 Altered Appetite and Weight: A weight loss of greater than 5 lbs occurred in 28% of
328 subjects receiving WELLBUTRIN. This incidence is approximately double that seen in
329 comparable subjects treated with tricyclics or placebo. Furthermore, while 35% of subjects
330 receiving tricyclic antidepressants gained weight, only 9.4% of subjects treated with
331 WELLBUTRIN did. Consequently, if weight loss is a major presenting sign of a patient's
332 depressive illness, the anorectic and/or weight reducing potential of WELLBUTRIN should be
333 considered.

334 **6.2 Postmarketing Experience**

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

339 Body (General): Arthralgia, myalgia, and fever with rash and other symptoms
340 suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness [*see*
341 *Warnings and Precautions (5.8)*].

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

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

346 Gastrointestinal: Esophagitis, hepatitis.

347 Hemic and Lymphatic: Ecchymosis, leukocytosis, leukopenia, thrombocytopenia.

348 Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications,
349 were observed when bupropion was coadministered with warfarin.

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

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

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

355 Special Senses: Tinnitus, increased intraocular pressure.

356 **7 DRUG INTERACTIONS**

357 **7.1 Potential for Other Drugs to Affect WELLBUTRIN**

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

361 Inhibitors of CYP2B6: *Ticlopidine and Clopidogrel:* Concomitant treatment with these
362 drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on

363 clinical response, dosage adjustment of WELLBUTRIN may be necessary when coadministered
364 with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see *Clinical Pharmacology (12.3)*].

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

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

374 **7.2 Potential for WELLBUTRIN to Affect Other Drugs**

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

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

388 **7.3 Drugs that Lower Seizure Threshold**

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

393 **7.4 Dopaminergic Drugs (Levodopa and Amantadine)**

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

399 **7.5 Use with Alcohol**

400 In postmarketing experience, there have been rare reports of adverse neuropsychiatric
401 events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with

402 WELLBUTRIN. The consumption of alcohol during treatment with WELLBUTRIN should be
403 minimized or avoided.

404 **7.6 MAO Inhibitors**

405 Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of
406 MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive
407 reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that
408 the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days
409 should elapse between discontinuation of an MAOI intended to treat depression and initiation of
410 treatment with WELLBUTRIN. Conversely, at least 14 days should be allowed after stopping
411 WELLBUTRIN before starting an MAOI antidepressant [see *Dosage and Administration (2.4,*
412 *2.5), Contraindications (4)*].

413 **7.7 Drug-Laboratory Test Interactions**

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

419 **8 USE IN SPECIFIC POPULATIONS**

420 **8.1 Pregnancy**

421 Pregnancy Category C

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

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

434 Human Data: Data from the international bupropion Pregnancy Registry (675 first-
435 trimester exposures) and a retrospective cohort study using the United Healthcare database
436 (1,213 first trimester exposures) did not show an increased risk for malformations overall.

437 No increased risk for cardiovascular malformations overall has been observed after
438 bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular
439 malformations in pregnancies with exposure to bupropion in the first trimester from the
440 international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first-trimester

441 maternal bupropion exposures), which is similar to the background rate of cardiovascular
442 malformations (approximately 1%). Data from the United Healthcare database and a case-control
443 study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular
444 malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an
445 increased risk for cardiovascular malformations overall after bupropion exposure during the first
446 trimester.

447 Study findings on bupropion exposure during the first trimester and risk for left
448 ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions
449 regarding a possible association. The United Healthcare database lacked sufficient power to
450 evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR =
451 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk
452 for LVOTO.

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

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

463 Animal Data: In studies conducted in rats and rabbits, bupropion was administered
464 orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively
465 (approximately 11 and 7 times the MRHD, respectively, on a mg/m² basis). No clear evidence of
466 teratogenic activity was found in either species; however, in rabbits, slightly increased incidences
467 of fetal malformations and skeletal variations were observed at the lowest dose tested (25
468 mg/kg/day, approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal
469 weights were observed at 50 mg/kg and greater.

470 When rats were administered bupropion at oral doses of up to 300 mg/kg/day
471 (approximately 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy
472 and lactation, there were no apparent adverse effects on offspring development.

473 **8.3 Nursing Mothers**

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

479 **8.4 Pediatric Use**

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

482 **8.5 Geriatric Use**

483 Of the approximately 6,000 subjects who participated in clinical trials with bupropion
484 sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥ 65 years and
485 47 were aged ≥ 75 years. In addition, several hundred subjects aged ≥ 65 years participated in
486 clinical trials using the immediate-release formulation of bupropion (depression trials). No
487 overall differences in safety or effectiveness were observed between these subjects and younger
488 subjects. Reported clinical experience has not identified differences in responses between the
489 elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled
490 out.

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

497 **8.6 Renal Impairment**

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

503 **8.7 Hepatic Impairment**

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

508 **9 DRUG ABUSE AND DEPENDENCE**

509 **9.1 Controlled Substance**

510 Bupropion is not a controlled substance.

511 **9.2 Abuse**

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

515 In a population of individuals experienced with drugs of abuse, a single oral dose of
516 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the
517 Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a
518 score greater than placebo but less than 15 mg of the Schedule II stimulant dextroamphetamine

519 on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug
520 liking which are often associated with abuse potential.

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

527 WELLBUTRIN is intended for oral use only. The inhalation of crushed tablets or
528 injection of dissolved bupropion has been reported. aSeizures and/or cases of death have been
529 reported when bupropion has been administered intranasally or by parenteral injection.

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

537 **10 OVERDOSAGE**

538 **10.1 Human Overdose Experience**

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

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

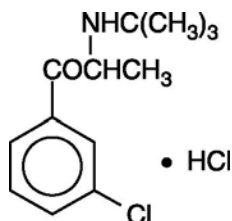
549 **10.2 Overdosage Management**

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

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

557 **11 DESCRIPTION**

558 WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class,
559 is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other
560 known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related
561 to phenylethylamines. It is designated as (\pm)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-
562 propanone hydrochloride. The molecular weight is 276.2. The molecular formula is
563 $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white, crystalline, and highly soluble in
564 water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The
565 structural formula is:



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

575 **12 CLINICAL PHARMACOLOGY**

576 **12.1 Mechanism of Action**

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

581 **12.3 Pharmacokinetics**

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

586 Absorption: The absolute bioavailability of WELLBUTRIN in humans has not been
587 determined because an intravenous formulation for human use is not available. However, it
588 appears likely that only a small proportion of any orally administered dose reaches the systemic
589 circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to
590 20%.

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

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

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

612 Following a single dose in humans, peak plasma concentrations of hydroxybupropion
613 occur approximately 3 hours after administration of WELLBUTRIN and are approximately
614 10 times the peak level of the parent drug at steady state. The elimination half-life of
615 hydroxybupropion is approximately 20 (\pm 5) hours, and its AUC at steady state is about 17 times
616 that of bupropion. The times to peak concentrations for the erythrohydrobupropion and
617 threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite.
618 However, their elimination half-lives are longer, 33 (\pm 10) and 37 (\pm 13) hours, respectively, and
619 steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

620 Bupropion and its metabolites exhibit linear kinetics following chronic administration of
621 300 to 450 mg per day.

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

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

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

646 *Hepatic Impairment:* The effect of hepatic impairment on the pharmacokinetics of
 647 bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease
 648 and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of
 649 hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in
 650 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically
 651 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
 652 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life
 653 for bupropion and the other metabolites in the 2 groups were minimal.

654 The second trial demonstrated no statistically significant differences in the
 655 pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild-to-moderate
 656 hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in
 657 some of the pharmacokinetic parameters for bupropion (AUC , C_{\max} , and T_{\max}) and its active
 658 metabolites ($t_{1/2}$) in subjects with mild-to-moderate hepatic cirrhosis. In subjects with severe
 659 hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites
 660 were seen (Table 3).

661

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

	C_{\max}	AUC	$t_{1/2}$	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

664 ^a = Difference.

665

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

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

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

685 *Smokers:* The effects of cigarette smoking on the pharmacokinetics of bupropion
686 were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and
687 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there
688 were no statistically significant differences in C_{max} , half-life, T_{max} , AUC, or clearance of
689 bupropion or its active metabolites between smokers and nonsmokers.

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

695 *Inhibitors of CYP2B6: Ticlopidine, Clopidogrel:* In a trial in healthy male
696 volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures
697 (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for
698 ticlopidine, respectively. The exposures (C_{max} and AUC) of hydroxybupropion were decreased
699 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This
700 effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

701 *Prasugrel:* Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects,
702 prasugrel increased bupropion C_{max} and AUC values by 14% and 18%, respectively, and
703 decreased C_{max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by
704 32% and 24%, respectively.

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

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

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

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

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

725 *Efavirenz:* In a trial in healthy volunteers, efavirenz 600 mg once daily for
726 2 weeks reduced the AUC and C_{max} of bupropion by approximately 55% and 34%, respectively.
727 The AUC of hydroxybupropion was unchanged, whereas C_{max} of hydroxybupropion was
728 increased by 50%.

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

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

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

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

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

748 **13 NONCLINICAL TOXICOLOGY**

749 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

750 Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up
751 to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the
752 MRHD, respectively, on a mg/m² basis. In the rat study there was an increase in nodular
753 proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the
754 MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such
755 lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions
756 were not seen in the mouse study, and no increase in malignant tumors of the liver and other
757 organs was seen in either study.

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

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

763 **14 CLINICAL STUDIES**

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

780

781 **Table 4. Efficacy of WELLBUTRIN 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-subtracted 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)	--

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

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

788 ^b Doses that are demonstrated to be statistically significantly superior to placebo.

789 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

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

794 Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between
 795 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Protect from light
 796 and moisture.

797 **17 PATIENT COUNSELING INFORMATION**

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

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

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

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

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

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

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

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

840 Angle-Closure Glaucoma: Patients should be advised that taking WELLBUTRIN can
841 cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-
842 closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-
843 closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle
844 glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to
845 determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g.,
846 iridectomy), if they are susceptible [*see Warnings and Precautions (5.7)*].

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

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

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

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

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

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

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

876
877 WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and ZYBAN are registered
878 trademarks of the GSK group of companies. The other brands listed are trademarks of their
879 respective owners and are not trademarks of the GSK group of companies. The makers of these
880 brands are not affiliated with and do not endorse the GSK group of companies or its products.

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885 Research Triangle Park, NC 27709

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

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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.

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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?”

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909

910

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

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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

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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.

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

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

938
939 **Call your healthcare provider right away if you or your family member has**
940 **any of the following symptoms, especially if they are new, worse, or worry**
941 **you:**
942

- 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

943
944 **What else do I need to know about antidepressant medicines?**

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

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

960
961 It is not known if WELLBUTRIN is safe and effective in children under the age of
962 18.

963
964 **Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and**
965 **Behavior, Depression, and Suicidal Thoughts or Actions**

966
967 This section of the Medication Guide is only about the risk of changes in thinking
968 and behavior, depression and suicidal thoughts or actions with drugs used to quit
969 smoking.

970
971 Although WELLBUTRIN is not a treatment for quitting smoking, it contains the
972 same active ingredient (bupropion hydrochloride) as ZYBAN[®] which is used to help
973 patients quit smoking.

974
975 Some people have had changes in behavior, hostility, agitation, depression,
976 suicidal thoughts or actions while taking bupropion to help them quit smoking.
977 These symptoms can develop during treatment with bupropion or after stopping
978 treatment with bupropion.

979
980 If you, your family member, or your caregiver notice agitation, hostility,
981 depression, or changes in thinking or behavior that are not typical for you, or you
982 have any of the following symptoms, stop taking bupropion and call your
983 healthcare provider right away:

984

- 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

985

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

993
994 Before taking bupropion, tell your healthcare provider if you have ever had
995 depression or other mental illnesses. You should also tell your healthcare provider
996 about any symptoms you had during other times you tried to quit smoking, with or
997 without bupropion.

998
999 **What Other Important Information Should I Know About WELLBUTRIN?**

- 1000 • **Seizures: There is a chance of having a seizure (convulsion, fit) with**
1001 **WELLBUTRIN, especially in people:**
1002 • with certain medical problems.
1003 • who take certain medicines.

1004
1005 The chance of having seizures increases with higher doses of WELLBUTRIN. For
1006 more information, see the sections “Who should not take WELLBUTRIN?” and
1007 “What should I tell my healthcare provider before taking WELLBUTRIN?” Tell your
1008 healthcare provider about all of your medical conditions and all the medicines you
1009 take. **Do not take any other medicines while you are taking WELLBUTRIN**
1010 **unless your healthcare provider has said it is okay to take them.**

1011
1012 **If you have a seizure while taking WELLBUTRIN, stop taking the tablets**
1013 **and call your healthcare provider right away.** Do not take WELLBUTRIN again
1014 if you have a seizure.

- 1015
1016 • **High blood pressure (hypertension). Some people get high blood**
1017 **pressure that can be severe, while taking WELLBUTRIN.** The chance of
1018 high blood pressure may be higher if you also use nicotine replacement therapy
1019 (such as a nicotine patch) to help you stop smoking.
1020 • **Manic episodes.** Some people may have periods of mania while taking
1021 WELLBUTRIN, including:
1022 • Greatly increased energy
1023 • Severe trouble sleeping
1024 • Racing thoughts
1025 • Reckless behavior

- 1026 • Unusually grand ideas
- 1027 • Excessive happiness or irritability
- 1028 • Talking more or faster than usual

1029 If you have any of the above symptoms of mania, call your healthcare provider.

- 1030 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or
- 1031 behaviors while taking WELLBUTRIN, including delusions (believe you are
- 1032 someone else), hallucinations (seeing or hearing things that are not there),
- 1033 paranoia (feeling that people are against you), or feeling confused. If this
- 1034 happens to you, call your healthcare provider.
- 1035 • **Visual problems.**
 - 1036 • eye pain
 - 1037 • changes in vision
 - 1038 • swelling or redness in or around the eye
- 1039 Only some people are at risk for these problems. You may want to undergo an
- 1040 eye examination to see if you are at risk and receive preventative treatment if
- 1041 you are.
- 1042 • **Severe allergic reactions. Some people can have severe allergic**
- 1043 **reactions to WELLBUTRIN. Stop taking WELLBUTRIN and call your**
- 1044 **healthcare provider right away** if you get a rash, itching, hives, fever,
- 1045 swollen lymph glands, painful sores in the mouth or around the eyes, swelling of
- 1046 the lips or tongue, chest pain, or have trouble breathing. These could be signs of
- 1047 a serious allergic reaction.

1048

1049 **What is WELLBUTRIN?**

1050 WELLBUTRIN is a prescription medicine used to treat adults with a certain type of

1051 depression called major depressive disorder.

1052

1053 **Who should not take WELLBUTRIN?**

1054 **Do not take WELLBUTRIN if you**

- 1055 • have or had a seizure disorder or epilepsy.
- 1056 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1057 • **are taking any other medicines that contain bupropion, including ZYBAN**
- 1058 **(used to help people stop smoking) APLENZIN[®], FORFIVO XL[™],**
- 1059 **WELLBUTRIN SR[®], or WELLBUTRIN XL[®].** Bupropion is the same active
- 1060 ingredient that is in WELLBUTRIN.
- 1061 • drink a lot of alcohol and abruptly stop drinking, or use medicines called
- 1062 sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines,
- 1063 and you stop using them all of a sudden.

- 1064 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or
1065 pharmacist if you are not sure if you take an MAOI, including the antibiotic
1066 linezolid.
- 1067 • do not take an MAOI within 2 weeks of stopping WELLBUTRIN unless directed
1068 to do so by your healthcare provider.
- 1069 • do not start WELLBUTRIN if you stopped taking an MAOI in the last 2 weeks
1070 unless directed to do so by your healthcare provider.
- 1071 • are allergic to the active ingredient in WELLBUTRIN, bupropion, or to any of the
1072 inactive ingredients. See the end of this Medication Guide for a complete list of
1073 ingredients in WELLBUTRIN.

1074

1075 **What should I tell my healthcare provider before taking WELLBUTRIN?**

1076 Tell your healthcare provider if you have ever had depression, suicidal thoughts or
1077 actions, or other mental health problems. See “Antidepressant Medicines,
1078 Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions.”

1079

1080 **Tell your healthcare provider about your other medical conditions including**
1081 **if you:**

- 1082 • have liver problems, especially cirrhosis of the liver.
- 1083 • have kidney problems.
- 1084 • have, or have had, an eating disorder, such as anorexia nervosa or bulimia.
- 1085 • have had a head injury.
- 1086 • have had a seizure (convulsion, fit).
- 1087 • have a tumor in your nervous system (brain or spine).
- 1088 • have had a heart attack, heart problems, or high blood pressure.
- 1089 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1090 • drink alcohol.
- 1091 • abuse prescription medicines or street drugs.
- 1092 • are pregnant or plan to become pregnant.
- 1093 • are breastfeeding. WELLBUTRIN passes into your milk in small amounts.

1094

1095 **Tell your healthcare provider about all the medicines you take**, including
1096 prescription, over-the-counter medicines, vitamins, and herbal supplements. Many
1097 medicines increase your chances of having seizures or other serious side effects if
1098 you take them while you are taking WELLBUTRIN.

1099

1100 **How should I take WELLBUTRIN?**

- 1101 • Take WELLBUTRIN exactly as prescribed by your healthcare provider.
- 1102 • Take WELLBUTRIN at the same time each day.
- 1103 • Take your doses of WELLBUTRIN at least 6 hours apart.

- 1104 • **Do not chew, cut, or crush WELLBUTRIN tablets.**
- 1105 • You may take WELLBUTRIN with or without food.
- 1106 • If you miss a dose, do not take an extra dose to make up for the dose you
- 1107 missed. Wait and take your next dose at the regular time. **This is very**
- 1108 **important.** Too much WELLBUTRIN can increase your chance of having a
- 1109 seizure.
- 1110 • If you take too much WELLBUTRIN, or overdose, call your local emergency room
- 1111 or poison control center right away.
- 1112 • **Do not take any other medicines while taking WELLBUTRIN unless your**
- 1113 **healthcare provider has told you it is okay.**
- 1114 • If you are taking WELLBUTRIN for the treatment of major depressive disorder, it
- 1115 may take several weeks for you to feel that WELLBUTRIN is working. Once you
- 1116 feel better, it is important to keep taking WELLBUTRIN exactly as directed by
- 1117 your healthcare provider. Call your healthcare provider if you do not feel
- 1118 WELLBUTRIN is working for you.
- 1119 • Do not change your dose or stop taking WELLBUTRIN without talking with your
- 1120 healthcare provider first.

1121

1122 **What should I avoid while taking WELLBUTRIN?**

- 1123 • Limit or avoid using alcohol during treatment with WELLBUTRIN. If you usually
- 1124 drink a lot of alcohol, talk with your healthcare provider before suddenly
- 1125 stopping. If you suddenly stop drinking alcohol, you may increase your risk of
- 1126 having seizures.
- 1127 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN
- 1128 affects you. WELLBUTRIN can affect your ability to do these things safely.

1129

1130 **What are possible side effects of WELLBUTRIN?**

1131 See **“What Other Important Information Should I Know About**

1132 **WELLBUTRIN?”**

1133 WELLBUTRIN can cause serious side effects.

1134 The most common side effects of WELLBUTRIN include:

- 1135 • Nervousness
- 1136 • Dry mouth
- 1137 • Constipation
- 1138 • Headache
- 1139 • Nausea or vomiting
- 1140 • Dizziness
- 1141 • Heavy sweating
- 1142 • Shakiness (tremor)
- 1143 • Trouble sleeping

- 1144 • Blurred vision
1145 • Fast heartbeat

1146
1147 If you have nausea, take your medicine with food. If you have trouble sleeping, do
1148 not take your medicine too close to bedtime.

1149 Tell your healthcare provider right away about any side effects that bother you.

1150
1151 These are not all the possible side effects of WELLBUTRIN. For more information,
1152 ask your healthcare provider or pharmacist.

1153
1154 Call your healthcare provider for medical advice about side effects. You may report
1155 side effects to FDA at 1-800-FDA-1088.

1156
1157 You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

1158
1159 **How should I store WELLBUTRIN?**

- 1160 • Store WELLBUTRIN at room temperature between 59°F and 86°F (15°C to
1161 30°C).
1162 • Keep WELLBUTRIN Tablets dry and out of the light.

1163
1164 **Keep WELLBUTRIN and all medicines out of the reach of children.**

1165
1166 **General Information about WELLBUTRIN.**

1167 Medicines are sometimes prescribed for purposes other than those listed in a
1168 Medication Guide. Do not use WELLBUTRIN for a condition for which it was not
1169 prescribed. Do not give WELLBUTRIN to other people, even if they have the same
1170 symptoms you have. It may harm them.

1171
1172 If you take a urine drug screening test, WELLBUTRIN may make the test result
1173 positive for amphetamines. If you tell the person giving you the drug screening
1174 test that you are taking WELLBUTRIN, they can do a more specific drug screening
1175 test that should not have this problem.

1176
1177 This Medication Guide summarizes important information about WELLBUTRIN. If
1178 you would like more information, talk with your healthcare provider. You can ask
1179 your healthcare provider or pharmacist for information about WELLBUTRIN that is
1180 written for healthcare professionals.

1181
1182 For more information about WELLBUTRIN, go to www.wellbutrin.com or call 1-888-
1183 825-5249.

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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.

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Manufactured for:



GlaxoSmithKline
Research Triangle Park, NC 27709

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December 2014
WLT: 10MG

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

Warnings and Precautions, Angle-Closure Glaucoma (5.7) 07/2014

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, 5.8)

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)
- Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7)

ADVERSE REACTIONS

Most common adverse reactions (incidence $\geq 5\%$ and $\geq 2\%$ 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*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 General Instructions for Use
- 2.2 Dose Adjustment in Patients with Hepatic Impairment
- 2.3 Dose Adjustment in Patients with Renal Impairment
- 2.4 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant
- 2.5 Use of WELLBUTRIN SR with Reversible MAOIs Such as Linezolid or Methylene Blue

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

5.3 Seizure

5.4 Hypertension

5.5 Activation of Mania/Hypomania

5.6 Psychosis and Other Neuropsychiatric Reactions

5.7 Angle-Closure Glaucoma

5.8 Hypersensitivity Reactions

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect WELLBUTRIN SR

7.2 Potential for WELLBUTRIN SR to Affect Other Drugs

7.3 Drugs that Lower Seizure Threshold

7.4 Dopaminergic Drugs (Levodopa and Amantadine)

7.5 Use with Alcohol

7.6 MAO Inhibitors

7.7 Drug-Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

10 OVERDOSAGE

10.1 Human Overdose Experience

10.2 Overdosage Management

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

1 FULL PRESCRIBING INFORMATION

2 WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC
3 REACTIONS

4

5 SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

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

15 NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR
16 SMOKING CESSATION

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

26 1 INDICATIONS AND USAGE

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

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

32 The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to
33 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial
34 [see *Clinical Studies (14)*].

35 **2 DOSAGE AND ADMINISTRATION**

36 **2.1 General Instructions for Use**

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

40 The usual adult target dose for WELLBUTRIN SR is 300 mg per day, given as 150 mg
41 twice daily. Initiate dosing with 150 mg per day given as a single daily dose in the morning.
42 After 3 days of dosing, the dose may be increased to the 300-mg-per-day target dose, given as
43 150 mg twice daily. There should be an interval of at least 8 hours between successive doses. A
44 maximum of 400 mg per day, given as 200 mg twice daily, may be considered for patients in
45 whom no clinical improvement is noted after several weeks of treatment at 300 mg per day. To
46 avoid high peak concentrations of bupropion and/or its metabolites, do not exceed 200 mg in any
47 single dose.

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

53 **2.2 Dose Adjustment in Patients with Hepatic Impairment**

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

58 **2.3 Dose Adjustment in Patients with Renal Impairment**

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

62 **2.4 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI)** 63 **Antidepressant**

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

68 **2.5 Use of WELLBUTRIN SR with Reversible MAOIs Such as Linezolid or** 69 **Methylene Blue**

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

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

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

88 **3 DOSAGE FORMS AND STRENGTHS**

- 89 • 100 mg – blue, round, biconvex, film-coated, sustained-release tablets printed with
90 “WELLBUTRIN SR 100”.
- 91 • 150 mg – purple, round, biconvex, film-coated, sustained-release tablets printed with
92 “WELLBUTRIN SR 150”.
- 93 • 200 mg – light pink, round, biconvex, film-coated, sustained-release tablets printed with
94 “WELLBUTRIN SR 200”.

95 **4 CONTRAINDICATIONS**

- 96 • WELLBUTRIN SR is contraindicated in patients with a seizure disorder.
- 97 • WELLBUTRIN SR is contraindicated in patients with a current or prior diagnosis of bulimia
98 or anorexia nervosa as a higher incidence of seizures was observed in such patients treated
99 with the immediate-release formulation of bupropion [see Warnings and Precautions (5.3)].
- 100 • WELLBUTRIN SR is contraindicated in patients undergoing abrupt discontinuation of
101 alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Warnings and
102 Precautions (5.3), Drug Interactions (7.3)].
- 103 • The use of MAOIs (intended to treat psychiatric disorders) concomitantly with
104 WELLBUTRIN SR or within 14 days of discontinuing treatment with WELLBUTRIN SR is
105 contraindicated. There is an increased risk of hypertensive reactions when WELLBUTRIN
106 SR is used concomitantly with MAOIs. The use of WELLBUTRIN SR within 14 days of
107 discontinuing treatment with an MAOI is also contraindicated. Starting WELLBUTRIN SR
108 in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is

109 contraindicated [*see Dosage and Administration (2.4, 2.5), Warnings and Precautions (5.4),*
110 *Drug Interactions (7.6)*].

- 111 • WELLBUTRIN SR is contraindicated in patients with known hypersensitivity to bupropion
112 or other ingredients of WELLBUTRIN SR. Anaphylactoid/anaphylactic reactions and
113 Stevens-Johnson syndrome have been reported [*see Warnings and Precautions (5.8)*].

114 **5 WARNINGS AND PRECAUTIONS**

115 **5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young** 116 **Adults**

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

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

131 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,
132 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24
133 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of
134 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of
135 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000
136 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency
137 toward an increase in the younger subjects for almost all drugs studied. There were differences in
138 absolute risk of suicidality across the different indications, with the highest incidence in MDD.
139 The risk differences (drug vs. placebo), however, were relatively stable within age strata and
140 across indications. These risk differences (drug-placebo difference in the number of cases of
141 suicidality per 1,000 subjects treated) are provided in Table 1.

142

143 **Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled**
 144 **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

145
 146 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials,
 147 but the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

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

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

175 **5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation**
176 **Treatment**

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

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

188 **5.3 Seizure**

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

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

206 Incidence of Seizure with Bupropion Use: When WELLBUTRIN SR is dosed up to
207 300 mg per day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to
208 approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg per day.

209 The risk of seizure can be reduced if the dose of WELLBUTRIN SR does not exceed
210 400 mg per day, given as 200 mg twice daily, and the titration rate is gradual.

211 **5.4 Hypertension**

212 Treatment with WELLBUTRIN SR can result in elevated blood pressure and
213 hypertension. Assess blood pressure before initiating treatment with WELLBUTRIN SR, and
214 monitor periodically during treatment. The risk of hypertension is increased if WELLBUTRIN

215 SR is used concomitantly with MAOIs or other drugs that increase dopaminergic or
216 noradrenergic activity [see *Contraindications (4)*].

217 Data from a comparative trial of the sustained-release formulation of bupropion HCl,
218 nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS,
219 and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent
220 hypertension in patients treated with the combination of sustained-release bupropion and NTS. In
221 this trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS
222 had treatment-emergent hypertension compared with 2.5%, 1.6%, and 3.1% of subjects treated
223 with sustained-release bupropion, NTS, and placebo, respectively. The majority of these subjects
224 had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of
225 sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study
226 medication discontinued due to hypertension compared with none of the subjects treated with
227 sustained-release bupropion or placebo. Monitoring of blood pressure is recommended in
228 patients who receive the combination of bupropion and nicotine replacement.

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

234 **5.5 Activation of Mania/Hypomania**

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

241 **5.6 Psychosis and Other Neuropsychiatric Reactions**

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

247 **5.7 Angle-Closure Glaucoma**

248 The pupillary dilation that occurs following use of many antidepressant drugs including
249 WELLBUTRIN SR may trigger an angle-closure attack in a patient with anatomically narrow
250 angles who does not have a patent iridectomy.

251 **5.8 Hypersensitivity Reactions**

252 Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion.
253 Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring
254 medical treatment. In addition, there have been rare, spontaneous postmarketing reports of

255 erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with
256 bupropion. Instruct patients to discontinue WELLBUTRIN SR and consult a healthcare provider
257 if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives,
258 chest pain, edema, and shortness of breath) during treatment.

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

261 **6 ADVERSE REACTIONS**

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

- 264 • Suicidal thoughts and behaviors in adolescents and young adults [*see Boxed Warning,*
265 *Warnings and Precautions (5.1)*]
- 266 • Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [*see Boxed*
267 *Warning, Warnings and Precautions (5.2)*]
- 268 • Seizure [*see Warnings and Precautions (5.3)*]
- 269 • Hypertension [*see Warnings and Precautions (5.4)*]
- 270 • Activation of mania or hypomania [*see Warnings and Precautions (5.5)*]
- 271 • Psychosis and other neuropsychiatric reactions [*see Warnings and Precautions (5.6)*]
- 272 • Angle-closure glaucoma [*see Warnings and Precautions (5.7)*]
- 273 • Hypersensitivity reactions [*see Warnings and Precautions (5.8)*]

274 **6.1 Clinical Trials Experience**

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

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

283

284 **Table 2. Treatment Discontinuations Due to Adverse Reactions in Placebo-Controlled**
285 **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%

286

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

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

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

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

297

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

Body System/ Adverse Reaction	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
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%	—

300 ^a Incidence based on the number of female subjects.

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

302

303 Other Adverse Reactions Observed During the Clinical Development of

304 Bupropion: In addition to the adverse reactions noted above, the following adverse reactions

305 have been reported in clinical trials with the sustained-release formulation of bupropion in

306 depressed subjects and in nondepressed smokers, as well as in clinical trials with the
307 immediate-release formulation of bupropion.

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

317 Adverse reactions are further categorized by body system and listed in order of
318 decreasing frequency according to the following definitions of frequency: Frequent adverse
319 reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions
320 are those occurring in 1/100 to 1/1,000 subjects, while rare events are those occurring in less than
321 1/1,000 subjects.

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

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

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

328 *Hemic and Lymphatic:* Infrequent was ecchymosis.

329 *Metabolic and Nutritional:* Infrequent were edema and peripheral edema.

330 *Musculoskeletal:* Infrequent were leg cramps.

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

334 *Respiratory:* Rare was bronchospasm.

335 *Special Senses:* Infrequent were accommodation abnormality and dry eye.

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

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

339

340 **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%

341
 342 In clinical trials conducted with the immediate-release formulation of bupropion, 35% of
 343 subjects receiving tricyclic antidepressants gained weight, compared with 9% of subjects treated
 344 with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of
 345 a patient’s depressive illness, the anorectic and/or weight-reducing potential of
 346 WELLBUTRIN SR should be considered.

347 **6.2 Postmarketing Experience**

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

352 **Body (General):** Arthralgia, myalgia, and fever with rash and other symptoms
 353 suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness [*see*
 354 *Warnings and Precautions (5.8)*].

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

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

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

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

365 **Metabolic and Nutritional:** Glycosuria.

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

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

372 **Respiratory:** Pneumonia.

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

375 Special Senses: Deafness, increased intraocular pressure, and mydriasis.
376 Urogenital: Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia,
377 menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

378 **7 DRUG INTERACTIONS**

379 **7.1 Potential for Other Drugs to Affect WELLBUTRIN SR**

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

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

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

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

398 **7.2 Potential for WELLBUTRIN SR to Affect Other Drugs**

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

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

412 **7.3 Drugs that Lower Seizure Threshold**

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

417 **7.4 Dopaminergic Drugs (Levodopa and Amantadine)**

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

423 **7.5 Use with Alcohol**

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

428 **7.6 MAO Inhibitors**

429 Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of
430 MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive
431 reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that
432 the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days
433 should elapse between discontinuation of an MAOI intended to treat depression and initiation of
434 treatment with WELLBUTRIN SR. Conversely, at least 14 days should be allowed after
435 stopping WELLBUTRIN SR before starting an MAOI antidepressant [see *Dosage and*
436 *Administration (2.4, 2.5), Contraindications (4)*].

437 **7.7 Drug-Laboratory Test Interactions**

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

443 **8 USE IN SPECIFIC POPULATIONS**

444 **8.1 Pregnancy**

445 Pregnancy Category C

446 Risk Summary: Data from epidemiological studies of pregnant women exposed to
447 bupropion in the first trimester indicate no increased risk of congenital malformations overall.
448 All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major
449 malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity
450 was found in reproductive developmental studies conducted in rats and rabbits; however, in
451 rabbits, slightly increased incidences of fetal malformations and skeletal variations were

452 observed at doses approximately equal to the maximum recommended human dose (MRHD) and
453 greater and decreased fetal weights were seen at doses twice the MRHD and greater.
454 WELLBUTRIN SR should be used during pregnancy only if the potential benefit justifies the
455 potential risk to the fetus.

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

458 Human Data: Data from the international bupropion Pregnancy Registry (675 first
459 trimester exposures) and a retrospective cohort study using the United Healthcare database
460 (1,213 first trimester exposures) did not show an increased risk for malformations overall.

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

471 Study findings on bupropion exposure during the first trimester and risk for left
472 ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions
473 regarding a possible association. The United Healthcare database lacked sufficient power to
474 evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR =
475 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk
476 for LVOTO.

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

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

487 Animal Data: In studies conducted in rats and rabbits, bupropion was administered
488 orally during the period of organogenesis at doses of up to 450 and 150 mg/kg/day, respectively
489 (approximately 11 and 7 times the MRHD, respectively, on a mg/m² basis). No clear evidence of
490 teratogenic activity was found in either species; however, in rabbits, slightly increased incidences
491 of fetal malformations and skeletal variations were observed at the lowest dose tested (25

492 mg/kg/day, approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal
493 weights were observed at 50 mg/kg and greater.

494 When rats were administered bupropion at oral doses of up to 300 mg/kg/day
495 (approximately 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy
496 and lactation, there were no apparent adverse effects on offspring development.

497 **8.3 Nursing Mothers**

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

503 **8.4 Pediatric Use**

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

506 **8.5 Geriatric Use**

507 Of the approximately 6,000 subjects who participated in clinical trials with bupropion
508 sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥65 years and
509 47 were aged ≥75 years. In addition, several hundred subjects aged ≥65 years participated in
510 clinical trials using the immediate-release formulation of bupropion (depression trials). No
511 overall differences in safety or effectiveness were observed between these subjects and younger
512 subjects. Reported clinical experience has not identified differences in responses between the
513 elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled
514 out.

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

521 **8.6 Renal Impairment**

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

527 **8.7 Hepatic Impairment**

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

532 **9 DRUG ABUSE AND DEPENDENCE**

533 **9.1 Controlled Substance**

534 Bupropion is not a controlled substance.

535 **9.2 Abuse**

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

539 In a population of individuals experienced with drugs of abuse, a single oral dose of
540 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the
541 Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a
542 score greater than placebo but less than 15mg of the Schedule II stimulant dextroamphetamine
543 on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug
544 liking which are often associated with abuse potential.

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

551 WELLBUTRIN SR is intended for oral use only. The inhalation of crushed tablets or
552 injection of dissolved bupropion has been reported.. Seizures and/or cases of death have been
553 reported when bupropion has been administered intranasally or by parenteral injection.

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

561 **10 OVERDOSAGE**

562 **10.1 Human Overdose Experience**

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

569 Although most patients recovered without sequelae, deaths associated with overdoses of
570 bupropion alone have been reported in patients ingesting large doses of the drug. Multiple

571 uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported
572 in these patients.

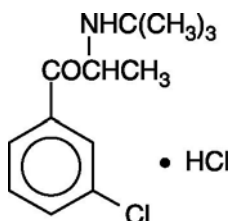
573 **10.2 Overdosage Management**

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

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

581 **11 DESCRIPTION**

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



590
591
592 WELLBUTRIN SR is supplied for oral administration as 100-mg (blue), 150-mg
593 (purple), and 200-mg (light pink), film-coated, sustained-release tablets. Each tablet contains the
594 labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine
595 hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene
596 glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the
597 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2
598 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

599 **12 CLINICAL PHARMACOLOGY**

600 **12.1 Mechanism of Action**

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

605 **12.3 Pharmacokinetics**

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

610 Absorption: The absolute bioavailability of WELLBUTRIN SR in humans has not been
611 determined because an intravenous formulation for human use is not available. However, it
612 appears likely that only a small proportion of any orally administered dose reaches the systemic
613 circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to
614 20%.

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

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

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

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

634 Metabolism: Bupropion is extensively metabolized in humans. Three metabolites are
635 active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of
636 bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion,
637 which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is
638 the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450
639 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion
640 side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is
641 then excreted as the major urinary metabolite. The potency and toxicity of the metabolites
642 relative to bupropion have not been fully characterized. However, it has been demonstrated in an
643 antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion,
644 while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion.

645 This may be of clinical importance because the plasma concentrations of the metabolites are as
646 high as or higher than those of bupropion.

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

655 Bupropion and its metabolites exhibit linear kinetics following chronic administration of
656 300 to 450 mg per day.

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

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

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

681 **Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of
682 bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease
683 and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of
684 hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in

685 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically
686 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
687 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life
688 for bupropion and the other metabolites in the 2 groups were minimal.

689 The second trial demonstrated no statistically significant differences in the
690 pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild-to-moderate
691 hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in
692 some of the pharmacokinetic parameters for bupropion (AUC , C_{max} , and T_{max}) and its active
693 metabolites ($t_{1/2}$) in subjects with mild-to-moderate hepatic cirrhosis. In subjects with severe
694 hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites
695 were seen (Table 5).

696

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

	C_{max}	AUC	$t_{1/2}$	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

699 ^a = Difference.

700

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

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

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

720 *Smokers:* The effects of cigarette smoking on the pharmacokinetics of bupropion
721 were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and
722 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there
723 were no statistically significant differences in C_{\max} , half-life, T_{\max} , AUC, or clearance of
724 bupropion or its active metabolites between smokers and nonsmokers.

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

730 *Inhibitors of CYP2B6: Ticlopidine, Clopidogrel:* In a trial in healthy male
731 volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures
732 (C_{\max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for
733 ticlopidine, respectively. The exposures (C_{\max} and AUC) of hydroxybupropion were decreased
734 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This
735 effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

736 *Prasugrel:* Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects,
737 prasugrel increased bupropion C_{\max} and AUC values by 14% and 18%, respectively, and
738 decreased C_{\max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by
739 32% and 24%, respectively.

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

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

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

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

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

760 *Efavirenz:* In a trial in healthy volunteers, efavirenz 600 mg once daily for
761 2 weeks reduced the AUC and C_{max} of bupropion by approximately 55% and 34%, respectively.
762 The AUC of hydroxybupropion was unchanged, whereas C_{max} of hydroxybupropion was
763 increased by 50%.

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

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

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

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

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

783 **13 NONCLINICAL TOXICOLOGY**

784 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

785 Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up
786 to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the
787 MRHD, respectively, on a mg/m² basis. In the rat study there was an increase in nodular
788 proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the
789 MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such
790 lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions
791 were not seen in the mouse study, and no increase in malignant tumors of the liver and other
792 organs was seen in either study.

793 Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of
794 5 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in
795 chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

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

798 **14 CLINICAL STUDIES**

799 The efficacy of the immediate-release formulation of bupropion in the treatment of major
800 depressive disorder was established in two 4-week, placebo-controlled trials in adult inpatients
801 with MDD (Trials 1 and 2 in Table 6) and in one 6-week, placebo-controlled trial in adult
802 outpatients with MDD (Trial 3 in Table 6). In the first trial, the dose range of bupropion was 300
803 mg to 600 mg per day administered in divided doses; 78% of subjects were treated with doses of
804 300 mg to 450 mg per day. This trial demonstrated the effectiveness of the immediate-release
805 formulation of bupropion by the Hamilton Depression Rating Scale (HDRS) total score, the
806 HDRS depressed mood item (item 1), and the Clinical Global Impressions severity score (CGI-
807 S). The second trial included 2 doses of the immediate-release formulation of bupropion (300
808 and 450 mg per day) and placebo. This trial demonstrated the effectiveness of the
809 immediate-release formulation of bupropion, but only at the 450-mg-per-day dose. The efficacy
810 results were significant for the HDRS total score and the CGI-S score, but not for HDRS item 1.
811 In the third trial, outpatients were treated with 300 mg per day of the immediate-release
812 formulation of bupropion. This trial demonstrated the efficacy of the immediate-release
813 formulation of bupropion as measured by the HDRS total score, the HDRS item 1, the
814 Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S score, and the CGI-
815 Improvement Scale (CGI-I) score.

816

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

Trial Number	Treatment Group	Primary Efficacy Measure: HDRS		
		Mean Baseline Score (SD)	LS Mean Score at Endpoint Visit (SE)	Placebo-subtracted 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)	--

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

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

825 ^b Doses that are demonstrated to be statistically significantly superior to placebo.
826

827 Although there are not as yet independent trials demonstrating the antidepressant
828 effectiveness of the sustained-release formulation of bupropion, trials have demonstrated the
829 bioequivalence of the immediate-release and sustained-release forms of bupropion under
830 steady-state conditions, i.e., bupropion sustained-release 150 mg twice daily was shown to be
831 bioequivalent to 100 mg 3 times daily of the immediate-release formulation of bupropion, with
832 regard to both rate and extent of absorption, for parent drug and metabolites.

833 In a longer-term trial, outpatients meeting DSM-IV criteria for major depressive disorder,
834 recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg
835 twice daily) were randomized to continuation of their same dose of WELLBUTRIN SR or
836 placebo for up to 44 weeks of observation for relapse. Response during the open phase was
837 defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of
838 the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's
839 judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving
840 continued treatment with WELLBUTRIN SR experienced significantly lower relapse rates over
841 the subsequent 44 weeks compared with those receiving placebo.

842 **16 HOW SUPPLIED/STORAGE AND HANDLING**

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

846 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are
847 purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of
848 60 (NDC 0173-0135-55) tablets.

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

852 Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between
853 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from light
854 and moisture.

855 **17 PATIENT COUNSELING INFORMATION**

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

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

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

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

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

881 **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment:**
882 Although WELLBUTRIN SR is not indicated for smoking cessation treatment, it contains the
883 same active ingredient as ZYBAN which is approved for this use. Advise patients, families and
884 caregivers that quitting smoking, with or without ZYBAN, may trigger nicotine withdrawal
885 symptoms (e.g., including depression or agitation), or worsen pre-existing psychiatric illness.
886 Some patients have experienced changes in mood (including depression and mania), psychosis,
887 hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as
888 suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while
889 taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking

890 or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they
891 should be urged to report these symptoms to their healthcare provider immediately.

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

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

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

901 **Angle-Closure Glaucoma:** Patients should be advised that taking WELLBUTRIN SR
902 can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of
903 angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because
904 angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-
905 angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be
906 examined to determine whether they are susceptible to angle closure, and have a prophylactic
907 procedure (e.g., iridectomy), if they are susceptible [*see Warnings and Precautions (5.7)*].

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

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

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

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

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

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

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

939
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952

953 **MEDICATION GUIDE**
954 **WELLBUTRIN[®] SR (WELL byu-trin)**
955 **(bupropion hydrochloride) Sustained-Release Tablets**
956

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

962
963 **IMPORTANT: Be sure to read the three sections of this Medication Guide.**
964 **The first section is about the risk of suicidal thoughts and actions with**
965 **antidepressant medicines; the second section is about the risk of changes**
966 **in thinking and behavior, depression and suicidal thoughts or actions with**

967 medicines used to quit smoking; and the third section is entitled “What
968 Other Important Information Should I Know About WELLBUTRIN SR?”

969
970 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses,**
971 **and Suicidal Thoughts or Actions**

972
973 This section of the Medication Guide is only about the risk of suicidal thoughts and
974 actions with antidepressant medicines. **Talk to your healthcare provider or your**
975 **family member’s healthcare provider about:**

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

978
979 **What is the most important information I should know about**
980 **antidepressant medicines, depression and other serious mental illnesses,**
981 **and suicidal thoughts or actions?**

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

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

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

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

1000
1001 **Call your healthcare provider right away if you or your family member has**
1002 **any of the following symptoms, especially if they are new, worse, or worry**
1003 **you:**

1004

- 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

1005

1006 **What else do I need to know about antidepressant medicines?**

- 1007 • **Never stop an antidepressant medicine without first talking to a**
- 1008 **healthcare provider.** Stopping an antidepressant medicine suddenly can cause
- 1009 other symptoms.
- 1010 • **Antidepressants are medicines used to treat depression and other**
- 1011 **illnesses.** It is important to discuss all the risks of treating depression and also
- 1012 the risks of not treating it. Patients and their families or other caregivers should
- 1013 discuss all treatment choices with the healthcare provider, not just the use of
- 1014 antidepressants.
- 1015 • **Antidepressant medicines have other side effects.** Talk to the healthcare
- 1016 provider about the side effects of the medicine prescribed for you or your family
- 1017 member.
- 1018 • **Antidepressant medicines can interact with other medicines.** Know all of
- 1019 the medicines that you or your family member takes. Keep a list of all medicines
- 1020 to show the healthcare provider. Do not start new medicines without first
- 1021 checking with your healthcare provider.

1022

1023 It is not known if WELLBUTRIN SR is safe and effective in children under the age of

1024 18.

1025

1026 **Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and**

1027 **Behavior, Depression, and Suicidal Thoughts or Actions**

1028

1029 This section of the Medication Guide is only about the risk of changes in thinking

1030 and behavior, depression and suicidal thoughts or actions with drugs used to quit

1031 smoking.

1032

1033 Although WELLBUTRIN SR is not a treatment for quitting smoking, it contains the

1034 same active ingredient (bupropion hydrochloride) as ZYBAN[®] which is used to help

1035 patients quit smoking.

1036

1037 Some people have had changes in behavior, hostility, agitation, depression, suicidal

1038 thoughts or actions while taking bupropion to help them quit smoking. These

1039 symptoms can develop during treatment with bupropion or after stopping treatment
1040 with bupropion.

1041
1042 If you, your family member, or your caregiver notice agitation, hostility,
1043 depression, or changes in thinking or behavior that are not typical for you, or you
1044 have any of the following symptoms, stop taking bupropion and call your healthcare
1045 provider right away:

- 1046
- 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

1047
1048 When you try to quit smoking, with or without bupropion, you may have symptoms
1049 that may be due to nicotine withdrawal, including urge to smoke, depressed mood,
1050 trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty
1051 concentrating, restlessness, decreased heart rate, and increased appetite or weight
1052 gain. Some people have even experienced suicidal thoughts when trying to quit
1053 smoking without medication. Sometimes quitting smoking can lead to worsening of
1054 mental health problems that you already have, such as depression.

1055
1056 Before taking bupropion, tell your healthcare provider if you have ever had
1057 depression or other mental illnesses. You should also tell your healthcare provider
1058 about any symptoms you had during other times you tried to quit smoking, with or
1059 without bupropion.

1060
1061 **What Other Important Information Should I Know About WELLBUTRIN SR?**

- 1062
- **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.

1067
1068 The chance of having seizures increases with higher doses of WELLBUTRIN SR.
1069 For more information, see the sections “Who should not take WELLBUTRIN SR?”

1070 and “What should I tell my healthcare provider before taking WELLBUTRIN SR?”
1071 Tell your healthcare provider about all of your medical conditions and all the
1072 medicines you take. **Do not take any other medicines while you are taking**
1073 **WELLBUTRIN SR unless your healthcare provider has said it is okay to**
1074 **take them.**

1075
1076 **If you have a seizure while taking WELLBUTRIN SR, stop taking the**
1077 **tablets and call your healthcare provider right away.** Do not take
1078 WELLBUTRIN SR again if you have a seizure.

1079
1080 • **High blood pressure (hypertension).** Some people get high blood
1081 **pressure, that can be severe, while taking WELLBUTRIN SR.** The chance
1082 of high blood pressure may be higher if you also use nicotine replacement
1083 therapy (such as a nicotine patch) to help you stop smoking.

1084 • **Manic episodes.** Some people may have periods of mania while taking
1085 WELLBUTRIN SR, including:

- 1086 • Greatly increased energy
- 1087 • Severe trouble sleeping
- 1088 • Racing thoughts
- 1089 • Reckless behavior
- 1090 • Unusually grand ideas
- 1091 • Excessive happiness or irritability
- 1092 • Talking more or faster than usual

1093 If you have any of the above symptoms of mania, call your healthcare provider.

1094 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or
1095 behaviors while taking WELLBUTRIN, including delusions (believe you are
1096 someone else), hallucinations (seeing or hearing things that are not there),
1097 paranoia (feeling that people are against you), or feeling confused. If this
1098 happens to you, call your healthcare provider.

1099 • **Visual problems.**

- 1100 • eye pain
- 1101 • changes in vision
- 1102 • swelling or redness in or around the eye

1103 Only some people are at risk for these problems. You may want to undergo an
1104 eye examination to see if you are at risk and receive preventative treatment if
1105 you are.

1106 • **Severe allergic reactions.** Some people can have severe allergic
1107 **reactions to WELLBUTRIN SR. Stop taking WELLBUTRIN SR and call your**
1108 **healthcare provider right away** if you get a rash, itching, hives, fever,
1109 swollen lymph glands, painful sores in the mouth or around the eyes, swelling of

1110 the lips or tongue, chest pain, or have trouble breathing. These could be signs of
1111 a serious allergic reaction.

1112

1113 **What is WELLBUTRIN SR?**

1114 WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type
1115 of depression called major depressive disorder.

1116

1117 **Who should not take WELLBUTRIN SR?**

1118 **Do not take WELLBUTRIN SR if you**

- 1119 • have or had a seizure disorder or epilepsy.
- 1120 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1121 • **are taking any other medicines that contain bupropion, ZYBAN (used to**
1122 **help people stop smoking) APLENZIN[®], FORFIVO XL[™], WELLBUTRIN[®], or**
1123 **WELLBUTRIN XL[®].** Bupropion is the same active ingredient that is in
1124 WELLBUTRIN SR.
- 1125 • drink a lot of alcohol and abruptly stop drinking, or use medicines called
1126 sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines,
1127 and you stop using them all of a sudden.
- 1128 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or
1129 pharmacist if you are not sure if you take an MAOI, including the antibiotic
1130 linezolid.
 - 1131 • do not take an MAOI within 2 weeks of stopping WELLBUTRIN SR unless
1132 directed to do so by your healthcare provider.
 - 1133 • do not start WELLBUTRIN SR if you stopped taking an MAOI in the last 2
1134 weeks unless directed to do so by your healthcare provider.
- 1135 • are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of
1136 the inactive ingredients. See the end of this Medication Guide for a complete list
1137 of ingredients in WELLBUTRIN SR.

1138

1139 **What should I tell my healthcare provider before taking WELLBUTRIN SR?**

1140 Tell your healthcare provider if you have ever had depression, suicidal thoughts or
1141 actions, or other mental health problems. See "Antidepressant Medicines,
1142 Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions."
1143

1144

1144 **Tell your healthcare provider about your other medical conditions including** 1145 **if you:**

- 1146 • have liver problems, especially cirrhosis of the liver.
- 1147 • have kidney problems.
- 1148 • have, or have had, an eating disorder, such as anorexia nervosa or bulimia.
- 1149 • have had a head injury.

- 1150 • have had a seizure (convulsion, fit).
- 1151 • have a tumor in your nervous system (brain or spine).
- 1152 • have had a heart attack, heart problems, or high blood pressure.
- 1153 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1154 • drink alcohol.
- 1155 • abuse prescription medicines or street drugs.
- 1156 • are pregnant or plan to become pregnant.
- 1157 • are breastfeeding. WELLBUTRIN passes into your milk in small amounts.
- 1158
- 1159 • **Tell your healthcare provider about all the medicines you take**, including
- 1160 prescription, over-the-counter medicines, vitamins, and herbal supplements.
- 1161 Many medicines increase your chances of having seizures or other serious side
- 1162 effects if you take them while you are taking WELLBUTRIN SR.
- 1163

1164 **How should I take WELLBUTRIN SR?**

- 1165 • Take WELLBUTRIN SR exactly as prescribed by your healthcare provider.
- 1166 • **Swallow WELLBUTRIN SR Tablets whole. Do not chew, cut, or crush**
- 1167 **WELLBUTRIN SR Tablets.** If you do, the medicine will be released into your
- 1168 body too quickly. If this happens you may be more likely to get side effects
- 1169 including seizures. **Tell your healthcare provider if you cannot swallow**
- 1170 **tablets.**
- 1171 • Take WELLBUTRIN SR at the same time each day.
- 1172 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 1173 • You may take WELLBUTRIN SR with or without food.
- 1174 • If you miss a dose, do not take an extra dose to make up for the dose you
- 1175 missed. Wait and take your next dose at the regular time. **This is very**
- 1176 **important.** Too much WELLBUTRIN SR can increase your chance of having a
- 1177 seizure.
- 1178 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency
- 1179 room or poison control center right away.
- 1180 • **Do not take any other medicines while taking WELLBUTRIN SR unless**
- 1181 **your healthcare provider has told you it is okay.**
- 1182 • If you are taking WELLBUTRIN SR for the treatment of major depressive
- 1183 disorder, it may take several weeks for you to feel that WELLBUTRIN SR is
- 1184 working. Once you feel better, it is important to keep taking WELLBUTRIN SR
- 1185 exactly as directed by your healthcare provider. Call your healthcare provider if
- 1186 you do not feel WELLBUTRIN SR is working for you.
- 1187 • Do not change your dose or stop taking WELLBUTRIN SR without talking with
- 1188 your healthcare provider first.
- 1189

1190 **What should I avoid while taking WELLBUTRIN SR?**

- 1191 • Limit or avoid using alcohol during treatment with WELLBUTRIN SR. If you
1192 usually drink a lot of alcohol, talk with your healthcare provider before suddenly
1193 stopping. If you suddenly stop drinking alcohol, you may increase your chance
1194 of having seizures.
- 1195 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR
1196 affects you. WELLBUTRIN SR can affect your ability to do these things safely.

1197

1198 **What are possible side effects of WELLBUTRIN SR?**

1199 See **“What Other Important Information Should I Know About**
1200 **WELLBUTRIN SR?”**

1201 WELLBUTRIN SR can cause serious side effects.

1202

1203 The most common side effects of WELLBUTRIN SR include:

- 1204 • Headache
1205 • Dry mouth
1206 • Nausea
1207 • Trouble sleeping
1208 • Dizziness
1209 • Sore throat
1210 • Constipation

1211

1212 If you have nausea, take your medicine with food. If you have trouble sleeping, do
1213 not take your medicine too close to bedtime.

1214

1215 Tell your healthcare provider right away about any side effects that bother you.

1216

1217 These are not all the possible side effects of WELLBUTRIN SR. For more
1218 information, ask your healthcare provider or pharmacist.

1219

1220 Call your doctor for medical advice about side effects. You may report side effects
1221 to FDA at 1-800-FDA-1088.

1222

1223 You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

1224

1225 **How should I store WELLBUTRIN SR?**

- 1226 • Store WELLBUTRIN SR at room temperature between 59°F and 86°F (15°C to
1227 30°C).
- 1228 • Keep WELLBUTRIN SR dry and out of the light.
- 1229 • WELLBUTRIN SR Tablets may have an odor.

1230
1231 **Keep WELLBUTRIN SR and all medicines out of the reach of children.**

1232
1233 **General Information about WELLBUTRIN SR.**

1234 Medicines are sometimes prescribed for purposes other than those listed in a
1235 Medication Guide. Do not use WELLBUTRIN SR for a condition for which it was not
1236 prescribed. Do not give WELLBUTRIN SR to other people, even if they have the
1237 same symptoms you have. It may harm them.

1238
1239 If you take a urine drug screening test, WELLBUTRIN SR may make the test result
1240 positive for amphetamines. If you tell the person giving you the drug screening test
1241 that you are taking WELLBUTRIN SR, they can do a more specific drug screening
1242 test that should not have this problem.

1243
1244 This Medication Guide summarizes important information about WELLBUTRIN SR. If
1245 you would like more information, talk with your healthcare provider. You can ask
1246 your healthcare provider or pharmacist for information about WELLBUTRIN SR that
1247 is written for healthcare professionals.

1248
1249 For more information about WELLBUTRIN SR, go to www.wellbutrin.com or call 1-
1250 888-825-5249.

1251
1252 **What are the ingredients in WELLBUTRIN SR?**

1253 Active ingredient: bupropion hydrochloride.

1254
1255 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose,
1256 magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80,
1257 and titanium dioxide. In addition, the 100-mg tablet contains FD&C Blue No. 1
1258 Lake, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake,
1259 and the 200-mg tablet contains FD&C Red No. 40 Lake. The tablets are printed with
1260 edible black ink.

1261
1262 This Medication Guide has been approved by the U.S. Food and Drug
1263 Administration.

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