

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

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1 FULL PRESCRIBING INFORMATION

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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.

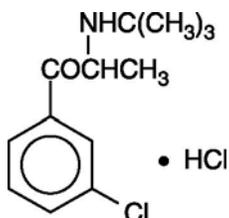
573 **10.2 Overdosage Management**

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 (\pm)-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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942 respective owners and are not trademarks of the GSK group of companies. The makers of these
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950
951 WLS:XXPIxPI
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

1063 • **Seizures: There is a chance of having a seizure (convulsion, fit) with**
1064 **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 **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.

1264
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1269 the GSK group of companies or its products.

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