

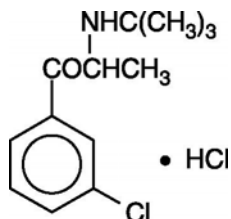
**WELLBUTRIN SR<sup>®</sup>**  
**(bupropion hydrochloride)**  
**Sustained-Release Tablets**

**Suicidality and Antidepressant Drugs**

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN SR or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. WELLBUTRIN SR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

**DESCRIPTION**

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



WELLBUTRIN SR Tablets are supplied for oral administration as 100-mg (blue), 150-mg (purple), and 200-mg (light pink), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine

36 hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene  
37 glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the  
38 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2  
39 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

## 40 **CLINICAL PHARMACOLOGY**

41 **Pharmacodynamics:** Bupropion is a relatively weak inhibitor of the neuronal uptake of  
42 norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of  
43 serotonin. While the mechanism of action of bupropion, as with other antidepressants, is  
44 unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic  
45 mechanisms.

46 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and  
47 pharmacokinetics of the individual enantiomers have not been studied. The mean elimination  
48 half-life ( $\pm$ SD) of bupropion after chronic dosing is 21 ( $\pm$ 9) hours, and steady-state plasma  
49 concentrations of bupropion are reached within 8 days. In a study comparing chronic dosing with  
50 WELLBUTRIN SR Tablets 150 mg twice daily to the immediate-release formulation of  
51 bupropion at 100 mg 3 times daily, peak plasma concentrations of bupropion at steady state for  
52 WELLBUTRIN SR Tablets were approximately 85% of those achieved with the  
53 immediate-release formulation. There was equivalence for bupropion AUCs, as well as  
54 equivalence for both peak plasma concentration and AUCs for all 3 of the detectable bupropion  
55 metabolites. Thus, at steady state, WELLBUTRIN SR Tablets, given twice daily, and the  
56 immediate-release formulation of bupropion, given 3 times daily, are essentially bioequivalent  
57 for both bupropion and the 3 quantitatively important metabolites.

58 **Absorption:** Following oral administration of WELLBUTRIN SR Tablets to healthy  
59 volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food  
60 increased  $C_{max}$  and AUC of bupropion by 11% and 17%, respectively, indicating that there is no  
61 clinically significant food effect.

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

66 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
67 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
68 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
69 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
70 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
71 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
72 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of  
73 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency  
74 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,

75 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is  
76 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-  
77 fold less potent than bupropion. This may be of clinical importance because the plasma  
78 concentrations of the metabolites are as high or higher than those of bupropion.

79 Because bupropion is extensively metabolized, there is the potential for drug-drug  
80 interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6  
81 (CYP2B6) isoenzyme. Although bupropion is not metabolized by cytochrome P450IID6  
82 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered  
83 with drugs metabolized by this isoenzyme (see PRECAUTIONS: Drug Interactions).

84 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur  
85 approximately 6 hours after administration of WELLBUTRIN SR Tablets. Peak plasma  
86 concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug  
87 at steady state. The elimination half-life of hydroxybupropion is approximately 20 ( $\pm$ 5) hours,  
88 and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations  
89 for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the  
90 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 ( $\pm$ 10) and 37  
91 ( $\pm$ 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,  
92 respectively.

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

95 **Elimination:** Following oral administration of 200 mg of  $^{14}$ C-bupropion in humans, 87% and  
96 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the  
97 fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent  
98 with the extensive metabolism of bupropion.

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

105 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was  
106 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in  
107 patients with mild to severe cirrhosis. The first study showed that the half-life of  
108 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in  
109 8 healthy volunteers (32 $\pm$ 14 hours versus 21 $\pm$ 5 hours, respectively). Although not statistically  
110 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be  
111 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for  
112 bupropion and the other metabolites in the 2 patient groups were minimal.

113 The second study showed no statistically significant differences in the pharmacokinetics of  
114 bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis

115 compared to 8 healthy volunteers. However, more variability was observed in some of the  
116 pharmacokinetic parameters for bupropion (AUC, C<sub>max</sub>, and T<sub>max</sub>) and its active metabolites (t<sub>1/2</sub>)  
117 in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic  
118 cirrhosis, the bupropion C<sub>max</sub> and AUC were substantially increased (mean difference: by  
119 approximately 70% and 3-fold, respectively) and more variable when compared to values in  
120 healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with  
121 severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion,  
122 the mean C<sub>max</sub> was approximately 69% lower. For the combined amino-alcohol isomers  
123 threohydrobupropion and erythrohydrobupropion, the mean C<sub>max</sub> was approximately 31% lower.  
124 The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for  
125 threo/erythrohydrobupropion. The median T<sub>max</sub> was observed 19 hours later for  
126 hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for  
127 hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively,  
128 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,  
129 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

130 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
131 renal impairment. An inter-study comparison between normal subjects and patients with end-  
132 stage renal failure demonstrated that the parent drug C<sub>max</sub> and AUC values were comparable in  
133 the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-  
134 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. The  
135 elimination of the major metabolites of bupropion may be reduced by impaired renal function  
136 (see PRECAUTIONS: Renal Impairment).

137 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in  
138 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on  
139 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed,  
140 compared to healthy volunteers.

141 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have not  
142 been fully characterized, but an exploration of steady-state bupropion concentrations from  
143 several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on  
144 a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma  
145 concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the  
146 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger  
147 subjects. These data suggest there is no prominent effect of age on bupropion concentration;  
148 however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly  
149 are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS:  
150 Geriatric Use).

151 **Gender:** A single-dose study involving 12 healthy male and 12 healthy female volunteers  
152 revealed no sex-related differences in the pharmacokinetic parameters of bupropion.

153 **Smokers:** The effects of cigarette smoking on the pharmacokinetics of bupropion were  
154 studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17

155 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there  
156 was no statistically significant difference in  $C_{max}$ , half-life,  $T_{max}$ , AUC, or clearance of bupropion  
157 or its active metabolites between smokers and nonsmokers.

## 158 **CLINICAL TRIALS**

159 The efficacy of the immediate-release formulation of bupropion as a treatment for depression  
160 was established in two 4-week, placebo-controlled trials in adult inpatients with depression and  
161 in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study,  
162 patients were titrated in a bupropion dose range of 300 to 600 mg/day on a 3 times daily  
163 schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial  
164 demonstrated the effectiveness of the immediate-release formulation of bupropion on the  
165 Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from  
166 that scale, and the Clinical Global Impressions (CGI) severity score. A second study included  
167 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and  
168 placebo. This trial demonstrated the effectiveness of the immediate-release formulation of  
169 bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS total score  
170 and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received  
171 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the  
172 effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS  
173 item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI  
174 improvement score.

175 Although there are not as yet independent trials demonstrating the antidepressant effectiveness  
176 of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence  
177 of the immediate-release and sustained-release forms of bupropion under steady-state conditions,  
178 i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 100 mg  
179 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and  
180 extent of absorption, for parent drug and metabolites.

181 In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder,  
182 recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg  
183 twice daily) were randomized to continuation of their same WELLBUTRIN SR dose or placebo,  
184 for up to 44 weeks of observation for relapse. Response during the open phase was defined as  
185 CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final  
186 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that  
187 drug treatment was needed for worsening depressive symptoms. Patients receiving continued  
188 WELLBUTRIN SR treatment experienced significantly lower relapse rates over the subsequent  
189 44 weeks compared to those receiving placebo.

## 190 **INDICATIONS AND USAGE**

191 WELLBUTRIN SR is indicated for the treatment of major depressive disorder.

192 The efficacy of bupropion in the treatment of a major depressive episode was established in  
193 two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of

194 depressed outpatients whose diagnoses corresponded most closely to the Major Depression  
195 category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL  
196 PHARMACOLOGY).

197 A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss  
198 of interest or pleasure; in addition, at least 5 of the following symptoms have been present during  
199 the same 2-week period and represent a change from previous functioning: depressed mood,  
200 markedly diminished interest or pleasure in usual activities, significant change in weight and/or  
201 appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue,  
202 feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt  
203 or suicidal ideation.

204 The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to  
205 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial  
206 (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use  
207 WELLBUTRIN SR for extended periods should periodically reevaluate the long-term usefulness  
208 of the drug for the individual patient.

## 209 **CONTRAINDICATIONS**

210 WELLBUTRIN SR is contraindicated in patients with a seizure disorder.

211 WELLBUTRIN SR is contraindicated in patients treated with ZYBAN<sup>®</sup> (bupropion  
212 hydrochloride) Sustained-Release Tablets; WELLBUTRIN<sup>®</sup> (bupropion hydrochloride), the  
213 immediate-release formulation; WELLBUTRIN XL<sup>®</sup> (bupropion hydrochloride), the extended-  
214 release formulation; or any other medications that contain bupropion because the incidence of  
215 seizure is dose dependent.

216 WELLBUTRIN SR is contraindicated in patients with a current or prior diagnosis of bulimia  
217 or anorexia nervosa because of a higher incidence of seizures noted in patients treated for  
218 bulimia with the immediate-release formulation of bupropion.

219 WELLBUTRIN SR is contraindicated in patients undergoing abrupt discontinuation of  
220 alcohol or sedatives (including benzodiazepines).

221 The concurrent administration of WELLBUTRIN SR Tablets and a monoamine oxidase  
222 (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an  
223 MAO inhibitor and initiation of treatment with WELLBUTRIN SR Tablets.

224 WELLBUTRIN SR is contraindicated in patients who have shown an allergic response to  
225 bupropion or the other ingredients that make up WELLBUTRIN SR Tablets.

## 226 **WARNINGS**

227 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),  
228 both adult and pediatric, may experience worsening of their depression and/or the emergence of  
229 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they  
230 are taking antidepressant medications, and this risk may persist until significant remission  
231 occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these  
232 disorders themselves are the strongest predictors of suicide. There has been a long-standing

233 concern, however, that antidepressants may have a role in inducing worsening of depression and  
 234 the emergence of suicidality in certain patients during the early phases of treatment. Pooled  
 235 analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others)  
 236 showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in  
 237 children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and  
 238 other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality  
 239 with antidepressants compared to placebo in adults beyond age 24; there was a reduction with  
 240 antidepressants compared to placebo in adults aged 65 and older.

241 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
 242 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24  
 243 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of  
 244 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of  
 245 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000  
 246 patients. There was considerable variation in risk of suicidality among drugs, but a tendency  
 247 toward an increase in the younger patients for almost all drugs studied. There were differences in  
 248 absolute risk of suicidality across the different indications, with the highest incidence in MDD.  
 249 The risk differences (drug vs placebo), however, were relatively stable within age strata and  
 250 across indications. These risk differences (drug-placebo difference in the number of cases of  
 251 suicidality per 1,000 patients treated) are provided in Table 1.

252  
 253

**Table 1**

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

254  
 255 No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but  
 256 the number was not sufficient to reach any conclusion about drug effect on suicide.

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

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

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

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

276 **Families and caregivers of patients being treated with antidepressants for major  
277 depressive disorder or other indications, both psychiatric and nonpsychiatric, should be  
278 alerted about the need to monitor patients for the emergence of agitation, irritability,  
279 unusual changes in behavior, and the other symptoms described above, as well as the  
280 emergence of suicidality, and to report such symptoms immediately to health care  
281 providers. Such monitoring should include daily observation by families and caregivers.**

282 Prescriptions for WELLBUTRIN SR should be written for the smallest quantity of tablets  
283 consistent with good patient management, in order to reduce the risk of overdose.

284 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial  
285 presentation of bipolar disorder. It is generally believed (though not established in controlled  
286 trials) that treating such an episode with an antidepressant alone may increase the likelihood of  
287 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the  
288 symptoms described above represent such a conversion is unknown. However, prior to initiating  
289 treatment with an antidepressant, patients with depressive symptoms should be adequately  
290 screened to determine if they are at risk for bipolar disorder; such screening should include a  
291 detailed psychiatric history, including a family history of suicide, bipolar disorder, and  
292 depression. It should be noted that WELLBUTRIN SR is not approved for use in treating bipolar  
293 depression.

294 **Patients should be made aware that WELLBUTRIN SR contains the same active  
295 ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that  
296 WELLBUTRIN SR should not be used in combination with ZYBAN, or any other  
297 medications that contain bupropion, such as WELLBUTRIN (bupropion hydrochloride),  
298 the immediate-release formulation or WELLBUTRIN XL (bupropion hydrochloride), the  
299 extended-release formulation.**

300  
301 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures  
302 is also related to patient factors, clinical situations, and concomitant medications, which  
303 must be considered in selection of patients for therapy with WELLBUTRIN SR.



304 **WELLBUTRIN SR should be discontinued and not restarted in patients who experience a**  
305 **seizure while on treatment.**

- 306 • **Dose: At doses of WELLBUTRIN SR up to a dose of 300 mg/day, the incidence of**  
307 **seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000)**  
308 **at the maximum recommended dose of 400 mg/day.**

309 **Data for the immediate-release formulation of bupropion revealed a seizure incidence**  
310 **of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients**  
311 **treated at doses in a range of 300 to 450 mg/day. The 450-mg/day upper limit of this**  
312 **dose range is close to the currently recommended maximum dose of 400 mg/day for**  
313 **WELLBUTRIN SR Tablets. This seizure incidence (0.4%) may exceed that of other**  
314 **marketed antidepressants and WELLBUTRIN SR Tablets up to 300 mg/day by as**  
315 **much as 4-fold. This relative risk is only an approximate estimate because no direct**  
316 **comparative studies have been conducted.**

317 **Additional data accumulated for the immediate-release formulation of bupropion**  
318 **suggested that the estimated seizure incidence increases almost tenfold between 450 and**  
319 **600 mg/day, which is twice the usual adult dose and one and one-half the maximum**  
320 **recommended daily dose (400 mg) of WELLBUTRIN SR Tablets. This**  
321 **disproportionate increase in seizure incidence with dose incrementation calls for**  
322 **caution in dosing.**

323 **Data for WELLBUTRIN SR Tablets revealed a seizure incidence of approximately**  
324 **0.1% (i.e., 3 of 3,100 patients followed prospectively) in patients treated at doses in a**  
325 **range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence**  
326 **observed in this study involving the sustained-release formulation of bupropion**  
327 **resulted from the different formulation or the lower dose used. However, as noted**  
328 **above, the immediate-release and sustained-release formulations are bioequivalent with**  
329 **regard to both rate and extent of absorption during steady state (the most pertinent**  
330 **condition to estimating seizure incidence), since most observed seizures occur under**  
331 **steady-state conditions.**

- 332 • **Patient factors: Predisposing factors that may increase the risk of seizure with**  
333 **bupropion use include history of head trauma or prior seizure, central nervous system**  
334 **(CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications**  
335 **that lower seizure threshold.**
- 336 • **Clinical situations: Circumstances associated with an increased seizure risk include,**  
337 **among others, excessive use of alcohol or sedatives (including benzodiazepines);**  
338 **addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and**  
339 **anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- 340 • **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants,**  
341 **theophylline, systemic steroids) are known to lower seizure threshold.**

342 **Recommendations for Reducing the Risk of Seizure:** Retrospective analysis of  
343 clinical experience gained during the development of bupropion suggests that the risk of  
344 seizure may be minimized if

- 345 • the total daily dose of WELLBUTRIN SR Tablets does *not* exceed 400 mg,
- 346 • the daily dose is administered twice daily, and
- 347 • the rate of incrementation of dose is gradual.
- 348 • No single dose should exceed 200 mg to avoid high peak concentrations of bupropion  
349 and/or its metabolites.

350 WELLBUTRIN SR should be administered with extreme caution to patients with a  
351 history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients  
352 treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic  
353 steroids, etc.) that lower seizure threshold.

354 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients  
355 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,  
356 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is  
357 likely to occur in such patients to a greater extent than usual. The dose should not exceed  
358 100 mg every day or 150 mg every other day in these patients (see CLINICAL  
359 PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

360 **Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there  
361 was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In  
362 dogs receiving large doses of bupropion chronically, various histologic changes were seen in the  
363 liver, and laboratory tests suggesting mild hepatocellular injury were noted.

## 364 PRECAUTIONS

365 **General: Agitation and Insomnia:** Patients in placebo-controlled trials with  
366 WELLBUTRIN SR Tablets experienced agitation, anxiety, and insomnia as shown in Table 2.

367  
368 **Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials**

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

369  
370 In clinical studies, these symptoms were sometimes of sufficient magnitude to require  
371 treatment with sedative/hypnotic drugs.

372 Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of  
373 patients treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 0.8%  
374 of patients treated with placebo.

375 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Depressed  
376 patients treated with an immediate-release formulation of bupropion or with WELLBUTRIN SR  
377 Tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including  
378 delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some  
379 cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

380 **Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic episodes  
381 in bipolar disorder patients during the depressed phase of their illness and may activate latent  
382 psychosis in other susceptible patients. WELLBUTRIN SR is expected to pose similar risks.

383 **Altered Appetite and Weight:** In placebo-controlled studies, patients experienced weight  
384 gain or weight loss as shown in Table 3.

385

386 **Table 3. Incidence of Weight Gain and Weight Loss 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%

387

388 In studies conducted with the immediate-release formulation of bupropion, 35% of patients  
389 receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the  
390 immediate-release formulation of bupropion. If weight loss is a major presenting sign of a  
391 patient's depressive illness, the anorectic and/or weight-reducing potential of  
392 WELLBUTRIN SR Tablets should be considered.

393 **Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by symptoms such  
394 as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported  
395 in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing  
396 reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated  
397 with bupropion. A patient should stop taking WELLBUTRIN SR and consult a doctor if  
398 experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives,  
399 chest pain, edema, and shortness of breath) during treatment.

400 Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed  
401 hypersensitivity have been reported in association with bupropion. These symptoms may  
402 resemble serum sickness.

403 **Cardiovascular Effects:** In clinical practice, hypertension, in some cases severe, requiring  
404 acute treatment, has been reported in patients receiving bupropion alone and in combination with  
405 nicotine replacement therapy. These events have been observed in both patients with and without  
406 evidence of preexisting hypertension.

407 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN<sup>®</sup>  
408 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-  
409 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher

410 incidence of treatment-emergent hypertension in patients treated with the combination of  
411 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the  
412 combination of sustained-release bupropion and NTS had treatment-emergent hypertension  
413 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,  
414 and placebo, respectively. The majority of these patients had evidence of preexisting  
415 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and  
416 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension  
417 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure  
418 is recommended in patients who receive the combination of bupropion and nicotine replacement.

419 There is no clinical experience establishing the safety of WELLBUTRIN SR Tablets in  
420 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care  
421 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed  
422 patients who had previously developed orthostatic hypotension while receiving tricyclic  
423 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with  
424 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine  
425 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in  
426 2 patients for exacerbation of baseline hypertension.

427 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients  
428 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.  
429 WELLBUTRIN SR should be used with caution in patients with hepatic impairment (including  
430 mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in  
431 patients with mild to moderate hepatic cirrhosis.

432 All patients with hepatic impairment should be closely monitored for possible adverse effects  
433 that could indicate high drug and metabolite levels (see CLINICAL PHARMACOLOGY,  
434 WARNINGS, and DOSAGE AND ADMINISTRATION).

435 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
436 patients with renal impairment. An inter-study comparison between normal subjects and patients  
437 with end-stage renal failure demonstrated that the parent drug  $C_{max}$  and AUC values were  
438 comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
439 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage  
440 renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are  
441 further metabolized and subsequently excreted by the kidneys. WELLBUTRIN SR should be  
442 used with caution in patients with renal impairment and a reduced frequency and/or dose should  
443 be considered as bupropion and the metabolites of bupropion may accumulate in such patients to  
444 a greater extent than usual. The patient should be closely monitored for possible adverse effects  
445 that could indicate high drug or metabolite levels.

446 **Information for Patients:** Prescribers or other health professionals should inform patients,  
447 their families, and their caregivers about the benefits and risks associated with treatment with  
448 WELLBUTRIN SR and should counsel them in its appropriate use. A patient Medication Guide  
449 about “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal

450 Thoughts or Actions” and other important information about using WELLBUTRIN SR is  
451 available for WELLBUTRIN SR. The prescriber or health professional should instruct patients,  
452 their families, and their caregivers to read the Medication Guide and should assist them in  
453 understanding its contents. Patients should be given the opportunity to discuss the contents of the  
454 Medication Guide and to obtain answers to any questions they may have. The complete text of  
455 the Medication Guide is reprinted at the end of this document.

456 Patients should be advised of the following issues and asked to alert their prescriber if these  
457 occur while taking WELLBUTRIN SR.

458 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers  
459 should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,  
460 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),  
461 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal  
462 ideation, especially early during antidepressant treatment and when the dose is adjusted up or  
463 down. Families and caregivers of patients should be advised to look for the emergence of such  
464 symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be  
465 reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in  
466 onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be  
467 associated with an increased risk for suicidal thinking and behavior and indicate a need for very  
468 close monitoring and possibly changes in the medication.

469 Patients should be made aware that WELLBUTRIN SR contains the same active ingredient  
470 found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN SR  
471 should not be used in combination with ZYBAN or any other medications that contain bupropion  
472 hydrochloride (such as WELLBUTRIN, the immediate-release formulation and WELLBUTRIN  
473 XL, the extended-release formulation).

474 As dose is increased during initial titration to doses above 150 mg/day, patients should be  
475 instructed to take WELLBUTRIN SR Tablets in 2 divided doses, preferably with at least 8 hours  
476 between successive doses, to minimize the risk of seizures.

477 Patients should be told that WELLBUTRIN SR should be discontinued and not restarted if  
478 they experience a seizure while on treatment.

479 Patients should be told that any CNS-active drug like WELLBUTRIN SR Tablets may impair  
480 their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently,  
481 until they are reasonably certain that WELLBUTRIN SR Tablets do not adversely affect their  
482 performance, they should refrain from driving an automobile or operating complex, hazardous  
483 machinery.

484 Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives  
485 (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower  
486 alcohol tolerance during treatment with WELLBUTRIN SR. Patients should be advised that the  
487 consumption of alcohol should be minimized or avoided.

488 Patients should be advised to inform their physicians if they are taking or plan to take any  
489 prescription or over-the-counter drugs. Concern is warranted because WELLBUTRIN SR  
490 Tablets and other drugs may affect each other's metabolism.

491 Patients should be advised to notify their physicians if they become pregnant or intend to  
492 become pregnant during therapy.

493 Patients should be advised to swallow WELLBUTRIN SR Tablets whole so that the release  
494 rate is not altered. Do not chew, divide, or crush tablets.

495 **Laboratory Tests:** There are no specific laboratory tests recommended.

496 **Drug Interactions:** Few systemic data have been collected on the metabolism of bupropion  
497 following concomitant administration with other drugs or, alternatively, the effect of  
498 concomitant administration of bupropion on the metabolism of other drugs.

499 Because bupropion is extensively metabolized, the coadministration of other drugs may affect  
500 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to  
501 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
502 interaction between WELLBUTRIN SR and drugs that are substrates or inhibitors of the  
503 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro  
504 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
505 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
506 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
507 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant  
508 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites  
509 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg  
510 WELLBUTRIN SR Tablets with and without 800 mg of cimetidine, the pharmacokinetics of  
511 bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases  
512 in the AUC and  $C_{max}$ , respectively, of the combined moieties of threohydrobupropion and  
513 erythrohydrobupropion.

514 While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g.,  
515 carbamazepine, phenobarbital, phenytoin).

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

518 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
519 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to  
520 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.  
521 Nevertheless, there may be the potential for clinically important alterations of blood levels of  
522 coadministered drugs.

523 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most  
524 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are  
525 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this  
526 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a  
527 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6

528 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of  
529 50 mg desipramine increased the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of  
530 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the  
531 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6  
532 has not been formally studied.

533 Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6  
534 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,  
535 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),  
536 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),  
537 should be approached with caution and should be initiated at the lower end of the dose range of  
538 the concomitant medication. If bupropion is added to the treatment regimen of a patient already  
539 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original  
540 medication should be considered, particularly for those concomitant medications with a narrow  
541 therapeutic index.

542 **MAO Inhibitors:** Studies in animals demonstrate that the acute toxicity of bupropion is  
543 enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS).

544 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
545 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
546 Administration of WELLBUTRIN SR Tablets to patients receiving either levodopa or  
547 amantadine concurrently should be undertaken with caution, using small initial doses and  
548 gradual dose increases.

549 **Drugs That Lower Seizure Threshold:** Concurrent administration of  
550 WELLBUTRIN SR Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline,  
551 systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme  
552 caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

553 **Nicotine Transdermal System:** (see PRECAUTIONS: Cardiovascular Effects).

554 **Alcohol:** In postmarketing experience, there have been rare reports of adverse  
555 neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol  
556 during treatment with WELLBUTRIN SR. The consumption of alcohol during treatment with  
557 WELLBUTRIN SR should be minimized or avoided (also see CONTRAINDICATIONS).

558 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies  
559 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These  
560 doses are approximately 7 and 2 times the maximum recommended human dose (MRHD),  
561 respectively, on a  $mg/m^2$  basis. In the rat study there was an increase in nodular proliferative  
562 lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a  
563  $mg/m^2$  basis); lower doses were not tested. The question of whether or not such lesions may be  
564 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen  
565 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in  
566 either study.

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

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

572 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. In studies conducted in rats and  
573 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively  
574 (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively,  
575 on a mg/m<sup>2</sup> basis), during the period of organogenesis. No clear evidence of teratogenic activity  
576 was found in either species; however, in rabbits, slightly increased incidences of fetal  
577 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,  
578 approximately equal to the MRHD on a mg/m<sup>2</sup> basis) and greater. Decreased fetal weights were  
579 seen at 50 mg/kg and greater.

580 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
581 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
582 there were no apparent adverse effects on offspring development.

583 One study has been conducted in pregnant women. This retrospective, managed-care database  
584 study assessed the risk of congenital malformations overall, and cardiovascular malformations  
585 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
586 malformations following exposure to other antidepressants in the first trimester and bupropion  
587 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
588 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
589 showed no greater risk for congenital malformations overall, or cardiovascular malformations  
590 specifically, following first trimester bupropion exposure compared to exposure to all other  
591 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of  
592 this study have not been corroborated. WELLBUTRIN SR should be used during pregnancy only  
593 if the potential benefit justifies the potential risk to the fetus.

594 To monitor fetal outcomes of pregnant women exposed to WELLBUTRIN SR,  
595 GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are  
596 encouraged to register patients by calling (800) 336-2176.

597 **Labor and Delivery:** The effect of WELLBUTRIN SR Tablets on labor and delivery in  
598 humans is unknown.

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

603 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established  
604 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Anyone  
605 considering the use of WELLBUTRIN SR in a child or adolescent must balance the potential  
606 risks with the clinical need.



607 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with  
608 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and  
609 over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in  
610 clinical trials using the immediate-release formulation of bupropion (depression studies). No  
611 overall differences in safety or effectiveness were observed between these subjects and younger  
612 subjects, and other reported clinical experience has not identified differences in responses  
613 between the elderly and younger patients, but greater sensitivity of some older individuals cannot  
614 be ruled out.

615 A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its  
616 metabolites in elderly subjects was similar to that of younger subjects; however, another  
617 pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased  
618 risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY).

619 Bupropion is extensively metabolized in the liver to active metabolites, which are further  
620 metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in  
621 patients with impaired renal function. Because elderly patients are more likely to have decreased  
622 renal function, care should be taken in dose selection, and it may be useful to monitor renal  
623 function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION).

#### 624 **ADVERSE REACTIONS** (See also WARNINGS and PRECAUTIONS.)

625 The information included under the Incidence in Controlled Trials subsection of ADVERSE  
626 REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR  
627 Tablets. Information on additional adverse events associated with the sustained-release  
628 formulation of bupropion in smoking cessation trials, as well as the immediate-release  
629 formulation of bupropion, is included in a separate section (see Other Events Observed During  
630 the Clinical Development and Postmarketing Experience of Bupropion).

#### 631 **Incidence in Controlled Trials With WELLBUTRIN SR: Adverse Events Associated** 632 **With Discontinuation of Treatment Among Patients Treated With**

633 **WELLBUTRIN SR Tablets:** In placebo-controlled clinical trials, 9% and 11% of patients  
634 treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 4% of patients  
635 treated with placebo discontinued treatment due to adverse events. The specific adverse events in  
636 these trials that led to discontinuation in at least 1% of patients treated with either 300 or  
637 400 mg/day of WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed  
638 in Table 4.

639

640 **Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials**

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

641

642 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**

643 **Treated With WELLBUTRIN SR Tablets:** Table 5 enumerates treatment-emergent adverse  
 644 events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR  
 645 Tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or  
 646 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo  
 647 group are included. Reported adverse events were classified using a COSTART-based  
 648 Dictionary.

649 Accurate estimates of the incidence of adverse events associated with the use of any drug are  
 650 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician  
 651 judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward  
 652 events in the course of usual medical practice where patient characteristics and other factors  
 653 differ from those that prevailed in the clinical trials. These incidence figures also cannot be  
 654 compared with those obtained from other clinical studies involving related drug products as each  
 655 group of drug trials is conducted under a different set of conditions.

656 Finally, it is important to emphasize that the tabulation does not reflect the relative severity  
 657 and/or clinical importance of the events. A better perspective on the serious adverse events  
 658 associated with the use of WELLBUTRIN SR Tablets is provided in the WARNINGS and  
 659 PRECAUTIONS sections.

660

661 **Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials\***

Body System/ Adverse Event	WELLBUTRIN SR	WELLBUTRIN SR	Placebo (n = 385)
	300 mg/day (n = 376)	400 mg/day (n = 114)	
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—

Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%

Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage <sup>†</sup>	0%	2%	—
Urinary tract infection	1%	0%	—

662 \* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day  
663 of WELLBUTRIN SR Tablets, but equally or more frequently in the placebo group, were:  
664 abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis,  
665 dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory  
666 disorder, rhinitis, and tooth disorder.

667 <sup>†</sup> Incidence based on the number of female patients.

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

669

670 ***Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials:***

671 Adverse events from Table 5 occurring in at least 5% of patients treated with  
672 WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed below for the  
673 300- and 400-mg/day dose groups.

674 ***WELLBUTRIN SR 300 mg/day:*** Anorexia, dry mouth, rash, sweating, tinnitus, and  
675 tremor.

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

679 **Other Events Observed During the Clinical Development and Postmarketing**

680 **Experience of Bupropion:** In addition to the adverse events noted above, the following  
681 events have been reported in clinical trials and postmarketing experience with the  
682 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,  
683 as well as in clinical trials and postmarketing clinical experience with the immediate-release  
684 formulation of bupropion.

685 Adverse events for which frequencies are provided below occurred in clinical trials with the  
686 sustained-release formulation of bupropion. The frequencies represent the proportion of patients  
687 who experienced a treatment-emergent adverse event on at least one occasion in  
688 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients  
689 who experienced an adverse event requiring discontinuation of treatment in an open-label  
690 surveillance study with WELLBUTRIN SR Tablets (n = 3,100). All treatment-emergent adverse

691 events are included except those listed in Tables 2 through 5, those events listed in other  
692 safety-related sections, those adverse events subsumed under COSTART terms that are either  
693 overly general or excessively specific so as to be uninformative, those events not reasonably  
694 associated with the use of the drug, and those events that were not serious and occurred in fewer  
695 than 2 patients. Events of major clinical importance are described in the WARNINGS and  
696 PRECAUTIONS sections of the labeling.

697 Events are further categorized by body system and listed in order of decreasing frequency  
698 according to the following definitions of frequency: Frequent adverse events are defined as those  
699 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
700 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

701 Adverse events for which frequencies are not provided occurred in clinical trials or  
702 postmarketing experience with bupropion. Only those adverse events not previously listed for  
703 sustained-release bupropion are included. The extent to which these events may be associated  
704 with WELLBUTRIN SR is unknown.

705 **Body (General):** Infrequent were chills, facial edema, musculoskeletal chest pain, and  
706 photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash  
707 and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble  
708 serum sickness (see PRECAUTIONS).

709 **Cardiovascular:** Infrequent were postural hypotension, stroke, tachycardia, and  
710 vasodilation. Rare was syncope. Also observed were complete atrioventricular block,  
711 extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS),  
712 myocardial infarction, phlebitis, and pulmonary embolism.

713 **Digestive:** Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis,  
714 glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of  
715 tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage,  
716 hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

717 **Endocrine:** Also observed were hyperglycemia, hypoglycemia, and syndrome of  
718 inappropriate antidiuretic hormone.

719 **Hemic and Lymphatic:** Infrequent was ecchymosis. Also observed were anemia,  
720 leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT  
721 and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were  
722 observed when bupropion was coadministered with warfarin.

723 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed  
724 was glycosuria.

725 **Musculoskeletal:** Infrequent were leg cramps. Also observed were muscle  
726 rigidity/fever/rhabdomyolysis and muscle weakness.

727 **Nervous System:** Infrequent were abnormal coordination, decreased libido,  
728 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,  
729 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also  
730 observed were abnormal electroencephalogram (EEG), akinesia, aggression, aphasia, coma,

731 delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome,  
732 hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid  
733 ideation, restlessness, and unmasking tardive dyskinesia.

734 **Respiratory:** Rare was bronchospasm. Also observed was pneumonia.

735 **Skin:** Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative  
736 dermatitis, and hirsutism.

737 **Special Senses:** Infrequent were accommodation abnormality and dry eye. Also observed  
738 were deafness, diplopia, increased intraocular pressure, and mydriasis.

739 **Urogenital:** Infrequent were impotence, polyuria, and prostate disorder. Also observed were  
740 abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection,  
741 salpingitis, urinary incontinence, urinary retention, and vaginitis.

## 742 **DRUG ABUSE AND DEPENDENCE**

743 **Controlled Substance Class:** Bupropion is not a controlled substance.

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

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

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

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

## 765 **OVERDOSAGE**

766 **Human Overdose Experience:** Overdoses of up to 30 g or more of bupropion have been  
767 reported. Seizure was reported in approximately one third of all cases. Other serious reactions  
768 reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus  
769 tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle

770 rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported  
771 mainly when bupropion was part of multiple drug overdoses.

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

776 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
777 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
778 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
779 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
780 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
781 symptomatic patients.

782 Activated charcoal should be administered. There is no experience with the use of forced  
783 diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion  
784 overdoses. No specific antidotes for bupropion are known.

785 Due to the dose-related risk of seizures with WELLBUTRIN SR, hospitalization following  
786 suspected overdose should be considered. Based on studies in animals, it is recommended that  
787 seizures be treated with intravenous benzodiazepine administration and other supportive  
788 measures, as appropriate.

789 In managing overdosage, consider the possibility of multiple drug involvement. The physician  
790 should consider contacting a poison control center for additional information on the treatment of  
791 any overdose. Telephone numbers for certified poison control centers are listed in the  
792 *Physicians' Desk Reference* (PDR).

## 793 **DOSAGE AND ADMINISTRATION**

794 **General Dosing Considerations:** It is particularly important to administer  
795 WELLBUTRIN SR Tablets in a manner most likely to minimize the risk of seizure (see  
796 WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness,  
797 and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary,  
798 these effects may be managed by temporary reduction of dose or the short-term administration of  
799 an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required  
800 beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses.  
801 If distressing, untoward effects supervene, dose escalation should be stopped.

802 WELLBUTRIN SR should be swallowed whole and not crushed, divided, or chewed.

803 **Initial Treatment:** The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day,  
804 given as 150 mg twice daily. Dosing with WELLBUTRIN SR Tablets should begin at  
805 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately  
806 tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made  
807 as early as day 4 of dosing. There should be an interval of at least 8 hours between successive  
808 doses.

809 **Increasing the Dosage Above 300 mg/day:** As with other antidepressants, the full  
810 antidepressant effect of WELLBUTRIN SR Tablets may not be evident until 4 weeks of  
811 treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg  
812 twice daily, may be considered for patients in whom no clinical improvement is noted after  
813 several weeks of treatment at 300 mg/day.

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

825 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN SR  
826 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should  
827 not exceed 100 mg every day or 150 mg every other day in these patients. WELLBUTRIN SR  
828 should be used with caution in patients with hepatic impairment (including mild to moderate  
829 hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with  
830 mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and  
831 PRECAUTIONS).

832 **Dosage Adjustment for Patients with Impaired Renal Function:** WELLBUTRIN SR  
833 should be used with caution in patients with renal impairment and a reduced frequency and/or  
834 dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

## 835 **HOW SUPPLIED**

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

839 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are  
840 purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of  
841 60 (NDC 0173-0135-55) tablets.

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

845 **Store at controlled room temperature, 20° to 25°C (68° to 77°F) [see USP]. Dispense in a**  
846 **tight, light-resistant container as defined in the USP.**

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**MEDICATION GUIDE**  
**WELLBUTRIN SR<sup>®</sup> (WELL byu-trin)**  
**(bupropion hydrochloride) Sustained-Release Tablets**

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

**IMPORTANT: Be sure to read both sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is entitled “What other important information should I know about WELLBUTRIN SR?”**

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

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

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

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

- 1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- 2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
  - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
  - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

892

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

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

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WELLBUTRIN SR has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

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**What other important information should I know about WELLBUTRIN SR?**

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**There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN SR, especially in people:**

- with certain medical problems.
- who take certain medicines.

915

The chance of having seizures increases with higher doses of WELLBUTRIN SR. For more information, see the sections "Who should not take WELLBUTRIN SR?" and "What should I tell my doctor before using WELLBUTRIN SR?" Tell your doctor about all of your medical

917

921 conditions and all the medicines you take. **Do not take any other medicines while you are**  
922 **using WELLBUTRIN SR unless your doctor has said it is okay to take them.**

923

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

926

### 927 **What is WELLBUTRIN SR?**

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

930

### 931 **Who should not take WELLBUTRIN SR?**

#### 932 **Do not take WELLBUTRIN SR if you**

- 933 • have or had a seizure disorder or epilepsy.
- 934 • **are taking ZYBAN<sup>®</sup> (used to help people stop smoking) or any other medicines that**  
935 **contain bupropion hydrochloride, such as WELLBUTRIN<sup>®</sup> Tablets or WELLBUTRIN**  
936 **XL<sup>®</sup> Extended-Release Tablets.** Bupropion is the same active ingredient that is in  
937 WELLBUTRIN SR.
- 938 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
939 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 940 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
941 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
942 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 943 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 944 • are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the  
945 inactive ingredients. See the end of this leaflet for a complete list of ingredients in  
946 WELLBUTRIN SR.

947

### 948 **What should I tell my doctor before using WELLBUTRIN SR?**

- 949 • **Tell your doctor about your medical conditions. Tell your doctor if you:**
  - 950 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN SR can  
951 harm your unborn baby. If you can use WELLBUTRIN SR while you are pregnant, talk  
952 to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - 953 • **are breastfeeding.** WELLBUTRIN SR passes through your milk. It is not known if  
954 WELLBUTRIN SR can harm your baby.
  - 955 • **have liver problems,** especially cirrhosis of the liver.
  - 956 • have kidney problems.
  - 957 • have an eating disorder such as anorexia nervosa or bulimia.
  - 958 • have had a head injury.
  - 959 • have had a seizure (convulsion, fit).
  - 960 • have a tumor in your nervous system (brain or spine).

- 961 • have had a heart attack, heart problems, or high blood pressure.
- 962 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 963 • drink a lot of alcohol.
- 964 • abuse prescription medicines or street drugs.
- 965 • **Tell your doctor about all the medicines you take**, including prescription and non-
- 966 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
- 967 chances of having seizures or other serious side effects if you take them while you are using
- 968 WELLBUTRIN SR.

969

#### 970 **How should I take WELLBUTRIN SR?**

- 971 • Take WELLBUTRIN SR exactly as prescribed by your doctor.
- 972 • **Do not chew, cut, or crush WELLBUTRIN SR Tablets.** You must swallow the tablets
- 973 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 974 • Take WELLBUTRIN SR at the same time each day.
- 975 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 976 • You may take WELLBUTRIN SR with or without food.
- 977 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
- 978 take your next tablet at the regular time. **This is very important.** Too much
- 979 WELLBUTRIN SR can increase your chance of having a seizure.
- 980 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or
- 981 poison control center right away.
- 982 • **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has**
- 983 **told you it is okay.**
- 984 • It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel
- 985 better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor.
- 986 Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- 987 • Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor
- 988 first.

989

#### 990 **What should I avoid while taking WELLBUTRIN SR?**

- 991 • Do not drink a lot of alcohol while taking WELLBUTRIN SR. If you usually drink a lot of
- 992 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking
- 993 alcohol, you may increase your chance of having seizures.
- 994 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects
- 995 you. WELLBUTRIN SR can impair your ability to perform these tasks.

996

#### 997 **What are possible side effects of WELLBUTRIN SR?**

- 998 • **Seizures.** Some patients get seizures while taking WELLBUTRIN SR. **If you have a seizure**
- 999 **while taking WELLBUTRIN SR, stop taking the tablets and call your doctor right**
- 1000 **away.** Do not take WELLBUTRIN SR again if you have a seizure.

- 1001 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
1002 severe, while taking WELLBUTRIN SR. The chance of high blood pressure may be  
1003 increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help  
1004 you stop smoking.
- 1005 • **Severe allergic reactions: Stop taking WELLBUTRIN SR and call your doctor right**  
1006 **away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the  
1007 mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble  
1008 breathing. These could be signs of a serious allergic reaction.
- 1009 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1010 taking WELLBUTRIN SR, including delusions (believe you are someone else),  
1011 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are  
1012 against you), or feeling confused. If this happens to you, call your doctor.

1013

1014 The most common side effects of WELLBUTRIN SR are loss of appetite, dry mouth, skin rash,  
1015 sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble  
1016 sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

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1018 If you have nausea, you may want to take your medicine with food. If you have trouble sleeping,  
1019 do not take your medicine too close to bedtime.

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1021 Tell your doctor right away about any side effects that bother you.

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1023 These are not all the side effects of WELLBUTRIN SR. For a complete list, ask your doctor or  
1024 pharmacist.

1025

### 1026 **How should I store WELLBUTRIN SR?**

- 1027 • Store WELLBUTRIN SR at room temperature. Store out of direct sunlight. Keep  
1028 WELLBUTRIN SR in its tightly closed bottle.
- 1029 • WELLBUTRIN SR tablets may have an odor.

1030

### 1031 **General Information about WELLBUTRIN SR.**

- 1032 • Medicines are sometimes prescribed for purposes other than those listed in a Medication  
1033 Guide. Do not use WELLBUTRIN SR for a condition for which it was not prescribed. Do  
1034 not give WELLBUTRIN SR to other people, even if they have the same symptoms you have.  
1035 It may harm them. Keep WELLBUTRIN SR out of the reach of children.

1036

1037 This Medication Guide summarizes important information about WELLBUTRIN SR. For more  
1038 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
1039 WELLBUTRIN SR that is written for health professionals.

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1041 **What are the ingredients in WELLBUTRIN SR?**

1042 Active ingredient: bupropion hydrochloride.

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1044 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1045 microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In  
1046 addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C  
1047 Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40  
1048 Lake. The tablets are printed with edible black ink.

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1050 \*The following are registered trademarks of their respective manufacturers: NARDIL<sup>®</sup>/Warner  
1051 Lambert Company; MARPLAN<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

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1053 **R<sub>x</sub> only**

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1055 This Medication Guide has been approved by the U.S. Food and Drug Administration.

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1057 June 2007

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