

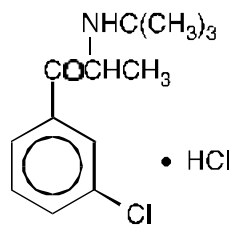
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PRODUCT INFORMATION

WELLBUTRIN SR[®]
(bupropion hydrochloride)
Sustained-Release Tablets

“Information for the Patient” enclosed.

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 C₁₃H₁₈ClNO•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:



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

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CLINICAL PHARMACOLOGY:

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

Pharmacokinetics: Bupropion is a racemic mixture. The pharmacologic activity and pharmacokinetics of the individual enantiomers have not been studied.

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35 Following oral administration of WELLBUTRIN SR Tablets to healthy volunteers, peak plasma
36 concentrations of bupropion are achieved within 3 hours. Food increased C_{max} and AUC of
37 bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food
38 effect.

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

43 Following oral administration of 200 mg of ¹⁴C-bupropion in humans, 87% and 10% of the
44 radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose
45 of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive
46 metabolism of bupropion.

47 The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 (\pm 9) hours, and
48 steady-state plasma concentrations of bupropion are reached within 8 days.

49 Bupropion is extensively metabolized in humans. Three metabolites have been shown to be
50 active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion,
51 and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are
52 formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome P450IIB6
53 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while
54 cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation
55 of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic
56 acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the
57 metabolites relative to bupropion have not been fully characterized. Nevertheless, they may be
58 clinically important because their plasma concentrations are higher than those of bupropion.

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

64 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur
65 approximately 6 hours after administration of WELLBUTRIN SR Tablets. Peak plasma
66 concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug
67 at steady state. The elimination half-life of hydroxybupropion is approximately 20 (\pm 5) hours, and
68 its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for
69 the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the
70 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (\pm 10) and 37
71 (\pm 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,
72 respectively.

73 In a study comparing chronic dosing with WELLBUTRIN SR Tablets 150 mg twice daily to the
74 immediate-release formulation of bupropion at 100 mg three times daily, peak plasma

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75 concentrations of bupropion at steady state for WELLBUTRIN SR Tablets were approximately
76 85% of those achieved with the immediate-release formulation. There was equivalence for
77 bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all
78 three of the detectable bupropion metabolites. Thus, at steady state, WELLBUTRIN SR Tablets,
79 given twice daily, and the immediate-release formulation of bupropion, given three times daily,
80 are essentially bioequivalent for both bupropion and the three quantitatively important metabolites.

81 Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to
82 450 mg/day.

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

89 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was
90 characterized in two single-dose studies, one in patients with alcoholic liver disease and one in
91 patients with mild to severe cirrhosis. The first study showed that the half-life of
92 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8
93 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically
94 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
95 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for
96 bupropion and the other metabolites in the two patient groups were minimal.

97 The second study showed that there were no statistically significant differences in the
98 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate
99 hepatic cirrhosis compared to 8 healthy volunteers. There was, however, more variability
100 observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its
101 active metabolites (t_{1/2}) in patients with mild to moderate hepatic cirrhosis. In addition, in patients
102 with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean
103 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to
104 values in healthy volunteers; the mean bupropion half-life was also longer (by approximately
105 40%). For the metabolites, the mean C_{max} was lower (by approximately 30% to 70%), the mean
106 AUC tended to be higher (by approximately 30% to 50%), the median T_{max} was later (by
107 approximately 20 hours), and the mean half-lives were longer (by approximately 2- to 4-fold) in
108 patients with severe hepatic cirrhosis than in healthy volunteers (see WARNINGS,
109 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

110 **Renal:** The effect of renal disease on the pharmacokinetics of bupropion has not been studied.
111 The elimination of the major metabolites of bupropion may be affected by reduced renal function.

112 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in 14
113 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray),

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114 no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to healthy
115 normal volunteers, was revealed.

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

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

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

132

133 **CLINICAL TRIALS:** The efficacy of the immediate-release formulation of bupropion as a
134 treatment for depression was established in two 4-week, placebo-controlled trials in adult
135 inpatients with depression and in one 6-week, placebo-controlled trial in adult outpatients with
136 depression. In the first study, patients were titrated in a bupropion dose range of 300 to
137 600 mg/day on a three times daily schedule; 78% of patients received maximum doses of
138 450 mg/day or less. This trial demonstrated the effectiveness of the immediate-release formulation
139 of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood
140 item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second
141 study included two fixed doses of the immediate-release formulation of bupropion (300 and
142 450 mg/day) and placebo. This trial demonstrated the effectiveness of the immediate-release
143 formulation of bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS
144 total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients
145 received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated
146 the effectiveness of the immediate-release formulation of bupropion on the HDRS total score,
147 HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the
148 CGI improvement score.

149 Although there are not as yet independent trials demonstrating the antidepressant effectiveness
150 of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence
151 of the immediate-release and sustained-release forms of bupropion under steady-state conditions,
152 i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 100 mg

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153 three times daily of the immediate-release formulation of bupropion, with regard to both rate and
154 extent of absorption, for parent drug and metabolites.

155 In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder,
156 recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg
157 twice daily) were randomized to continuation of their same WELLBUTRIN SR dose or placebo,
158 for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI
159 Improvement score of 1 (very much improved) or 2 (much improved) for each of the final three
160 weeks. Relapse during the double-blind phase was defined as the investigator's judgement that
161 drug treatment was needed for worsening depressive symptoms. Patients receiving continued
162 WELLBUTRIN SR treatment experienced significantly lower relapse rates over the subsequent
163 44 weeks compared to those receiving placebo.

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165 **INDICATIONS AND USAGE:** WELLBUTRIN SR is indicated for the treatment of depression.

166 The efficacy of bupropion in the treatment of depression was established in two 4-week
167 controlled trials of depressed inpatients and in one 6-week controlled trial of depressed
168 outpatients whose diagnoses corresponded most closely to the Major Depression category of the
169 APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

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

177 The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to
178 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial
179 (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use
180 WELLBUTRIN SR for extended periods should periodically reevaluate the long-term usefulness
181 of the drug for the individual patient.

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183 **CONTRAINDICATIONS:** WELLBUTRIN SR is contraindicated in patients with a seizure
184 disorder.

185 WELLBUTRIN SR is contraindicated in patients treated with ZYBAN[®] (bupropion
186 hydrochloride) Sustained-Release Tablets, or any other medications that contain bupropion
187 because the incidence of seizure is dose dependent.

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

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

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

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197 **WARNINGS:** Patients should be made aware that WELLBUTRIN SR contains the same
198 active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that
199 WELLBUTRIN SR should not be used in combination with ZYBAN, or any other medications
200 that contain bupropion.

201 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures is
202 also related to patient factors, clinical situations, and concomitant medications, which must be
203 considered in selection of patients for therapy with WELLBUTRIN SR. WELLBUTRIN SR
204 should be discontinued and not restarted in patients who experience a seizure while on
205 treatment.

- 206 • **Dose:** At doses of WELLBUTRIN SR up to a dose of 300 mg/day, the incidence of
207 seizure is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at
208 the maximum recommended dose of 400 mg/day.

209 Data for the immediate-release formulation of bupropion revealed a seizure incidence
210 of approximately 0.4% (i.e., 13 of 3200 patients followed prospectively) in patients
211 treated at doses in a range of 300 to 450 mg/day. The 450-mg/day upper limit of this dose
212 range is close to the currently recommended maximum dose of 400 mg/day for
213 WELLBUTRIN SR Tablets. This seizure incidence (0.4%) may exceed that of other
214 marketed antidepressants and WELLBUTRIN SR Tablets up to 300 mg/day by as much
215 as fourfold. This relative risk is only an approximate estimate because no direct
216 comparative studies have been conducted.

217 Additional data accumulated for the immediate-release formulation of bupropion
218 suggested that the estimated seizure incidence increases almost tenfold between 450 and
219 600 mg/day, which is twice the usual adult dose and one and one-half the maximum
220 recommended daily dose (400 mg) of WELLBUTRIN SR Tablets. This disproportionate
221 increase in seizure incidence with dose incrementation calls for caution in dosing.

222 Data for WELLBUTRIN SR Tablets revealed a seizure incidence of approximately
223 0.1% (i.e., 3 of 3100 patients followed prospectively) in patients treated at doses in a
224 range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence
225 observed in this study involving the sustained-release formulation of bupropion resulted
226 from the different formulation or the lower dose used. However, as noted above, the
227 immediate-release and sustained-release formulations are bioequivalent with regard to
228 both rate and extent of absorption during steady state (the most pertinent condition to
229 estimating seizure incidence), since most observed seizures occur under steady-state
230 conditions.

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- 231 • **Patient factors:** Predisposing factors that may increase the risk of seizure with bupropion
232 use include history of head trauma or prior seizure, central nervous system (CNS) tumor,
233 the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure
234 threshold.
- 235 • **Clinical situations:** Circumstances associated with an increased seizure risk include,
236 among others, excessive use of alcohol; abrupt withdrawal from alcohol or other
237 sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants
238 and anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 239 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,
240 theophylline, systemic steroids) and treatment regimens (e.g., abrupt discontinuation of
241 benzodiazepines) are known to lower seizure threshold.

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

- 245 • the total daily dose of WELLBUTRIN SR Tablets does *not* exceed 400 mg,
246 • the daily dose is administered twice daily, and
247 • the rate of incrementation of dose is gradual.
- 248 • No single dose should exceed 200 mg to avoid high peak concentrations of bupropion
249 and/or its metabolites.

250 WELLBUTRIN SR should be administered with extreme caution to patients with a
251 history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients
252 treated with other agents (e.g., antipsychotics, other antidepressants, theophylline,
253 systemic steroids, etc.) or treatment regimens (e.g., abrupt discontinuation of a
254 benzodiazepine) that lower seizure threshold.

255 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients
256 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,
257 as peak bupropion levels are substantially increased and accumulation is likely to occur in
258 such patients to a greater extent than usual. The dose should not exceed 100 mg every day or
259 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY,
260 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

265 PRECAUTIONS:

266 **General: Agitation and Insomnia:** Patients in placebo-controlled trials with
267 WELLBUTRIN SR Tablets experienced agitation, anxiety, and insomnia as shown in Table 1.
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270 **Table 1: 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%

271
272 In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment
273 with sedative/hypnotic drugs.

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

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

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

285 **Altered Appetite and Weight:** In placebo-controlled studies, patients experienced weight
286 gain or weight loss as shown in Table 2.

287
288 **Table 2: 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%

289
290 In studies conducted with the immediate-release formulation of bupropion, 35% of patients
291 receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the
292 immediate-release formulation of bupropion. If weight loss is a major presenting sign of a
293 patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN SR
294 Tablets should be considered.

295 **Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until
296 significant remission occurs. Accordingly, prescriptions for WELLBUTRIN SR Tablets should be
297 written for the smallest number of tablets consistent with good patient management.

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

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

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

312 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN[®]
313 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-
314 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher
315 incidence of treatment-emergent hypertension in patients treated with the combination of sustained-
316 release bupropion and NTS. In this study, 6.1% of patients treated with the combination of
317 sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%,
318 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo,
319 respectively. The majority of these patients had evidence of preexisting hypertension. Three
320 patients (1.2%) treated with the combination of ZYBAN and NTS and one patient (0.4%) treated
321 with NTS had study medication discontinued due to hypertension compared to none of the patients
322 treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who
323 receive the combination of bupropion and nicotine replacement.

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

332 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients
333 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.
334 WELLBUTRIN SR should be used with caution in patients with hepatic impairment (including
335 mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in
336 patients with mild to moderate hepatic cirrhosis.

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

340 **Renal Impairment:** No studies have been conducted in patients with renal impairment.
341 Bupropion is extensively metabolized in the liver to active metabolites, which are further
342 metabolized and excreted by the kidneys. WELLBUTRIN SR should be used with caution in
343 patients with renal impairment and a reduced frequency and/or dose should be considered as
344 bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The
345 patient should be closely monitored for possible adverse effects that could indicate high drug or
346 metabolite levels

347 **Information for Patients:** See the tear-off leaflet at the end of this labeling for Information for
348 the Patient.

349 Patients should be made aware that WELLBUTRIN SR contains the same active ingredient
350 found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN SR
351 should not be used in combination with ZYBAN or any other medications that contain bupropion
352 hydrochloride.

353 Physicians are advised to discuss the following issues with patients:

354 As dose is increased during initial titration to doses above 150 mg/day, patients should be
355 instructed to take WELLBUTRIN SR Tablets in two divided doses, preferably with at least
356 8 hours between successive doses, to minimize the risk of seizures.

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

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

364 Patients should be told that the use and cessation of use of alcohol may alter the seizure
365 threshold, and, therefore, that the consumption of alcohol should be minimized, and, if possible,
366 avoided completely.

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

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

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

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

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375 **Drug Interactions:** Few systemic data have been collected on the metabolism of
376 WELLBUTRIN SR following concomitant administration with other drugs or, alternatively, the
377 effect of concomitant administration of WELLBUTRIN SR on the metabolism of other drugs.

378 Because bupropion is extensively metabolized, the coadministration of other drugs may affect
379 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to
380 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction
381 between WELLBUTRIN SR and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and
382 cyclophosphamide). The threohydrobupropion metabolite of bupropion does not appear to be
383 produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of
384 cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24
385 healthy young male volunteers. Following oral administration of two 150-mg WELLBUTRIN SR
386 Tablets with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and
387 hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and
388 C_{max} respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

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

391 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
392 humans. In one study, following chronic administration of bupropion, 100 mg three times daily to
393 eight healthy male volunteers for 14 days, there was no evidence of induction of its own
394 metabolism. Nevertheless, there may be the potential for clinically important alterations of blood
395 levels of coadministered drugs.

396 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most
397 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are
398 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme,
399 bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15
400 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme,
401 daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg
402 desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of approximately two-,
403 five-, and two-fold, respectively. The effect was present for at least 7 days after the last dose of
404 bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been
405 formally studied.

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

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

417 **Levodopa:** Limited clinical data suggest a higher incidence of adverse experiences in patients
418 receiving concurrent administration of bupropion and levodopa. Administration of
419 WELLBUTRIN SR Tablets to patients receiving levodopa concurrently should be undertaken with
420 caution, using small initial doses and gradual dose increases.

421 **Drugs That Lower Seizure Threshold:** Concurrent administration of WELLBUTRIN SR
422 Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids,
423 etc.) or treatment regimens (e.g., abrupt discontinuation of benzodiazepines) that lower seizure
424 threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing
425 and gradual dose increases should be employed.

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

427 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies
428 were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These
429 doses are approximately seven and two times the maximum recommended human dose (MRHD),
430 respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative
431 lesions of the liver at doses of 100 to 300 mg/kg per day (approximately two to seven times the
432 MRHD on a mg/m² basis); lower doses were not tested. The question of whether or not such
433 lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions
434 were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs
435 was seen in either study.

436 Bupropion produced a positive response (two to three times control mutation rate) in two of
437 five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in
438 one of three in vivo rat bone marrow cytogenetic studies.

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

440 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Teratology studies have been
441 performed at doses up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately
442 7 to 11 and 7 times the MRHD, respectively, on a mg/m² basis), and have revealed no evidence of
443 harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant
444 women. Because animal reproduction studies are not always predictive of human response, this
445 drug should be used during pregnancy only if clearly needed.

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

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

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

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455 **Pediatric Use:** The safety and effectiveness of WELLBUTRIN SR Tablets in pediatric patients
456 below 18 years old have not been established. The immediate-release formulation of bupropion
457 was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other
458 indications. Although generally well tolerated, the limited exposure is insufficient to assess the
459 safety of bupropion in pediatric patients.

460 **Geriatric Use:** Of the approximately 6000 patients who participated in clinical trials with
461 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and
462 over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in
463 clinical trials using the immediate-release formulation of bupropion (depression studies). No
464 overall differences in safety or effectiveness were observed between these subjects and younger
465 subjects, and other reported clinical experience has not identified differences in responses
466 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
467 be ruled out.

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

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

477

478 **ADVERSE REACTIONS:** (See also WARNINGS and PRECAUTIONS).

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

485 **Incidence in Controlled Trials With WELLBUTRIN SR: Adverse Events Associated
486 With Discontinuation of Treatment Among Patients Treated With**

487 **WELLBUTRIN SR Tablets:** In placebo-controlled clinical trials, 9% and 11% of patients
488 treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 4% of patients
489 treated with placebo discontinued treatment due to adverse events. The specific adverse events in
490 these trials that led to discontinuation in at least 1% of patients treated with either 300 or
491 400 mg/day of WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed in
492 Table 3.

493

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494 **Table 3: Treatment Discontinuations Due to Adverse Events in Placebo-Controlled**
 495 **Trials**

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
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%

496

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

498 **Treated With WELLBUTRIN SR Tablets:** Table 4 enumerates treatment-emergent adverse
 499 events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR
 500 Tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or
 501 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo
 502 group are included. Reported adverse events were classified using a COSTART-based
 503 Dictionary.

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

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

515

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516

Table 4: Treatment-Emergent Adverse Events in Placebo-Controlled Trials*

Body System/ Adverse Event	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%

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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%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage [†]	0%	2%	—
Urinary tract infection	1%	0%	—

517 * Adverse events that occurred in at least 1% of patients treated with either 300 or
518 400 mg/day of WELLBUTRIN SR Tablets, but equally or more frequently in the placebo
519 group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain,
520 bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain,
521 respiratory disorder, rhinitis, and tooth disorder.

522 [†] Incidence based on the number of female patients.

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

524

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

526 Adverse events from Table 4 occurring in at least 5% of patients treated with WELLBUTRIN SR
527 Tablets and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day
528 dose groups.

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

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

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

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

539 Adverse events for which frequencies are provided below occurred in clinical trials with the
540 sustained-release formulation of bupropion. The frequencies represent the proportion of patients
541 who experienced a treatment-emergent adverse event on at least one occasion in
542 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1013), or patients
543 who experienced an adverse event requiring discontinuation of treatment in an open-label
544 surveillance study with WELLBUTRIN SR Tablets (n = 3100). All treatment-emergent adverse
545 events are included except those listed in Tables 1 through 4, those events listed in other
546 safety-related sections, those adverse events subsumed under COSTART terms that are either
547 overly general or excessively specific so as to be uninformative, those events not reasonably
548 associated with the use of the drug, and those events that were not serious and occurred in fewer
549 than two patients. Events of major clinical importance are described in the WARNINGS and
550 PRECAUTIONS sections of the labeling.

551 Events are further categorized by body system and listed in order of decreasing frequency
552 according to the following definitions of frequency: Frequent adverse events are defined as those
553 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
554 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

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

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

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

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

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

573 **Hemic and Lymphatic:** Infrequent was ecchymosis. Also observed were anemia,
574 leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.

575 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed
576 was glycosuria.

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

579 **Nervous System:** Infrequent were abnormal coordination, decreased libido,
580 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
581 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also
582 observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium,
583 dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased
584 libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive
585 dyskinesia.

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

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

589 **Special Senses:** Infrequent were accommodation abnormality and dry eye. Also observed
590 were deafness, diplopia, and mydriasis.

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

594

595 **DRUG ABUSE AND DEPENDENCE:**

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

597 **Humans:** Controlled clinical studies of bupropion conducted in normal volunteers, in subjects
598 with a history of multiple drug abuse, and in depressed patients showed some increase in motor
599 activity and agitation/excitement.

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

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

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

617

618 **OVERDOSAGE:**

619 **Human Overdose Experience:** There has been very limited experience with overdosage of
620 WELLBUTRIN SR Tablets; three cases were reported during clinical trials. One patient ingested
621 3000 mg of WELLBUTRIN SR Tablets and vomited quickly after the overdose; the patient
622 experienced blurred vision and lightheadedness. A second patient ingested a "handful" of
623 WELLBUTRIN SR Tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A
624 third patient ingested 3600 mg of WELLBUTRIN SR Tablets and a bottle of wine; the patient
625 experienced nausea, visual hallucinations, and "grogginess." None of the patients experienced
626 further sequelae.

627 There has been extensive experience with overdosage of the immediate-release formulation of
628 bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to
629 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of the
630 immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand
631 mal seizure and recovered without further sequelae.

632 Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of
633 bupropion have been reported. Seizure was reported in approximately one third of all cases. Other
634 serious reactions reported with overdoses of the immediate-release formulation of bupropion
635 alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity,
636 rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the
637 immediate-release formulation of bupropion was part of multiple drug overdoses.

638 Although most patients recovered without sequelae, deaths associated with overdoses of the
639 immediate-release formulation of bupropion alone have been reported rarely in patients ingesting
640 massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and
641 cardiac arrest prior to death were reported in these patients.

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

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

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

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

659

DOSAGE AND ADMINISTRATION:

660 **General Dosing Considerations:** It is particularly important to administer WELLBUTRIN SR
661 Tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual
662 escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen
663 during the initial days of treatment, are to be minimized. If necessary, these effects may be
664 managed by temporary reduction of dose or the short-term administration of an intermediate to
665 long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of
666 treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward
667 effects supervene, dose escalation should be stopped. WELLBUTRIN SR should be swallowed
668 whole and not crushed, divided, or chewed.

670 **Initial Treatment:** The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day,
671 given as 150 mg twice daily. Dosing with WELLBUTRIN SR Tablets should begin at 150 mg/day
672 given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an
673 increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made as early as day
674 4 of dosing. There should be an interval of at least 8 hours between successive doses.

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

680 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require
681 several months or longer of sustained pharmacological therapy beyond response to the acute
682 episode. In a study in which patients with major depressive disorder, recurrent type, who had
683 responded during 8 weeks of acute treatment with WELLBUTRIN SR were assigned randomly to
684 placebo or to the same dose of WELLBUTRIN SR (150 mg twice daily) during 44 weeks of
685 maintenance treatment as they had received during the acute stabilization phase, longer-term
686 efficacy was demonstrated (see CLINICAL TRIALS under CLINICAL PHARMACOLOGY).
687 Based on these limited data, it is unknown whether or not the dose of WELLBUTRIN SR needed

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688 for maintenance treatment is identical to the dose needed to achieve an initial response. Patients
689 should be periodically reassessed to determine the need for maintenance treatment and the
690 appropriate dose for such treatment.

691 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN SR
692 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not
693 exceed 100 mg every day or 150 mg every other day in these patients. WELLBUTRIN SR should
694 be used with caution in patients with hepatic impairment (including mild to moderate hepatic
695 cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to
696 moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and
697 PRECAUTIONS).

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

701

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

705 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple,
706 round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of 60 (NDC
707 0173-0135-55) tablets.

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

711

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

714

715



716

717 Distributed by:

718 GlaxoSmithKline, Research Triangle Park, NC 27709

719

720 Manufactured by:

721 GlaxoSmithKline

722 Research Triangle Park, NC 27709

723 or

724 Catalytica Pharmaceuticals, Inc.

725 Greenville, NC 27834

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(Date of Issue) RL-

PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

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Information for the Patient

WELLBUTRIN SR[®] (bupropion hydrochloride) Sustained-Release Tablets

737 Please read this information before you start taking WELLBUTRIN SR. Also read this leaflet each
738 time you renew your prescription, in case anything has changed. This information is not intended to
739 take the place of discussions between you and your doctor. You and your doctor should discuss
740 WELLBUTRIN SR as it relates to the treatment of your depression. Do not let anyone else use
741 your WELLBUTRIN SR.

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743

IMPORTANT WARNING:

744 At a dose of up to 300 mg each day, there is a chance that approximately 1 out of every 1000
745 people taking bupropion hydrochloride, the active ingredient in WELLBUTRIN SR, will have a
746 seizure. At a dose of 400 mg each day, there is a chance that approximately 4 out of every 1000
747 people will have a seizure. The chance of this happening increases if you:

- 748 • have or have had a seizure disorder (for example, epilepsy);
- 749 • have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- 750 • take more than the recommended amount of WELLBUTRIN SR; or
- 751 • take other medicines with the same active ingredient that is in WELLBUTRIN SR, such as
752 ZYBAN[®] (bupropion hydrochloride) Sustained-Release Tablets (used to help people quit
753 smoking).

754 You can reduce the chance of experiencing a seizure by following your doctor's directions on
755 how to take WELLBUTRIN SR. If you experience a seizure while taking WELLBUTRIN SR, stop
756 taking the tablets immediately, contact your doctor, and do not restart WELLBUTRIN SR. In
757 addition, tell your doctor if you have or have had other medical conditions. You should also
758 discuss with your doctor whether WELLBUTRIN SR is right for you.

759
760

1. What is WELLBUTRIN SR?

761 WELLBUTRIN SR is a prescription medicine used to treat depression.

2. Who should not take WELLBUTRIN SR?

762 You should not take WELLBUTRIN SR if you:
763

WELLBUTRIN SR[®] (bupropion hydrochloride) Sustained-Release Tablets

- 764 • have or have had a seizure disorder (for example, epilepsy);
765 • are already taking ZYBAN or any other medicines that contain bupropion hydrochloride;
766 • have or have had an eating disorder (for example, bulimia or anorexia nervosa);
767 • are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI); or
768 • are allergic to bupropion.

769 **3. Are there special concerns for women?**

770 WELLBUTRIN SR is not recommended for women who are pregnant or breast-feeding. Women
771 should notify their doctor if they become pregnant or intend to become pregnant while taking
772 WELLBUTRIN SR.

773 **4. Are there any concerns for patients with liver or kidney problems?**

774 If you have liver or kidney problems, tell your doctor before taking WELLBUTRIN SR.
775 Depending on the severity of your condition, your doctor may need to adjust your dosage.

776 **5. How should I take WELLBUTRIN SR?**

- 777 • You should take WELLBUTRIN SR as directed by your doctor. The usual recommended
778 dosing is to begin treatment with WELLBUTRIN SR by taking one 150-mg tablet in the
779 morning. As early as day 4 of treatment, your doctor may increase your dose to one 150-mg
780 tablet in the morning and one 150-mg tablet in the early evening (for a total of 300 mg each
781 day).

782 If your depression does not improve after several weeks, your doctor may increase the dose
783 of WELLBUTRIN SR to a total of 400 mg each day (taken as 200 mg in the morning and
784 200 mg in the early evening). Doses should be taken at least 8 hours apart.

- 785 • **Never take an “extra” dose of WELLBUTRIN SR Tablets for any reason, even if you**
786 **miss a dose.** If you forget to take a dose, do not take an extra tablet to “catch up” for the dose
787 you forgot. Wait and take your next tablet at the regular time. Do not take more tablets than your
788 doctor prescribed. This is important so you do not increase your chance of having a seizure.
789 • It is important to swallow WELLBUTRIN SR Tablets whole. Do not chew, divide, or crush
790 tablets.

791 **6. How long should I take WELLBUTRIN SR?**

792 Only you and your doctor can determine how long you should take WELLBUTRIN SR. You and
793 your doctor should discuss your signs and symptoms of depression regularly to determine how
794 long you should take WELLBUTRIN SR. Do not stop taking your medicine or decrease the amount
795 of medicine you are taking without talking to your doctor first.

796 **7. What are possible side effects of WELLBUTRIN SR?**

797 Like all medicines, WELLBUTRIN SR may cause side effects. Do not rely on this summary
798 alone for information about side effects. Your doctor can discuss with you a more complete list of
799 side effects that may be relevant to you.

- 800 • Hypertension (high blood pressure), in some cases severe, has been reported in patients taking
801 WELLBUTRIN SR alone and in combination with nicotine replacement therapy (for example,
802 a nicotine patch) used to help patients stop smoking. Tell your doctor if you are using or plan

WELLBUTRIN SR[®] (bupropion hydrochloride) Sustained-Release Tablets

803 to use nicotine replacement therapy because your doctor will probably want to check your
804 blood pressure regularly to make sure that it stays within acceptable levels.

805 • The most common side effects of WELLBUTRIN SR in clinical studies were:

806 At 300 mg/day: Loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, and
807 shakiness.

808 At 400 mg/day: Abdominal (stomach) pain, agitation, anxiety, dizziness, dry mouth, difficulty
809 sleeping, muscle pain, nausea, rapid heart beat, sore throat, sweating, ringing in the ears, and
810 urinating more often.

811 • The side effects of WELLBUTRIN SR are generally mild and often disappear after a few
812 weeks. If you have nausea, you may want to take your medicine with food. If you have
813 difficulty sleeping, avoid taking your medicine too close to bedtime.

814 • The most common side effects that caused people to stop taking WELLBUTRIN SR during
815 clinical studies were skin rash, nausea, agitation, and migraine (a severe type of headache).

816 • Stop taking WELLBUTRIN SR and contact your doctor or health care professional if you have
817 signs of an allergic reaction such as a skin rash, or difficulty in breathing. It is not possible to
818 predict whether a mild rash will develop into a more serious reaction. Therefore, if you
819 experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or
820 around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms
821 may be the first signs of a serious reaction. Discuss any other troublesome side effects with
822 your doctor.

823 • Use caution before driving a car or operating complex, hazardous machinery until you know if
824 WELLBUTRIN SR affects your ability to perform these tasks.

825 **8. Will taking WELLBUTRIN SR change my body weight?**

826 In clinical studies with WELLBUTRIN SR, some people lost weight and other people gained
827 weight.

828 For people who lost weight, 14 out of 100 people taking 300 mg/day of WELLBUTRIN SR lost
829 more than 5 lbs, 19 out of 100 people taking 400 mg/day lost more than 5 lbs, and 6 out of 100
830 people taking placebo (a sugar pill) lost more than 5 lbs.

831 For people who gained weight, 3 out of 100 people taking 300 mg/day of WELLBUTRIN SR
832 gained more than 5 lbs, 2 out of 100 people taking 400 mg/day gained more than 5 lbs, and 4 out of
833 100 people taking placebo (a sugar pill) gained more than 5 lbs.

834 Since weight change (loss or gain) also can be a symptom of depression, you should discuss
835 with your doctor whether WELLBUTRIN SR is right for you.

836 **9. Should I drink alcohol while I am taking WELLBUTRIN SR?**

837 It is best to not drink alcohol at all or to drink very little while taking WELLBUTRIN SR. If you
838 usually drink a lot of alcohol, or if you drink a lot of alcohol and suddenly stop, you may increase
839 your chance of having a seizure. Therefore, it is important to discuss your use of alcohol with your
840 doctor before you begin taking WELLBUTRIN SR.

841 **10. Will WELLBUTRIN SR affect other medicines I am taking?**

WELLBUTRIN SR[®] (bupropion hydrochloride) Sustained-Release Tablets

842 WELLBUTRIN SR may affect other medicines you're taking. It is important not to take
843 medicines that may increase the chance for you to have a seizure. Therefore, you should make sure
844 that your doctor knows about all medicines—prescription and over-the-counter—you are taking or
845 plan to take.

846 **11. Do WELLBUTRIN SR Tablets have a characteristic odor?**

847 WELLBUTRIN SR Tablets may have a characteristic odor. If present, this odor is normal.

848 **12. How should I store WELLBUTRIN SR?**

- 849 • Store WELLBUTRIN SR at room temperature, out of direct sunlight.
- 850 • Keep WELLBUTRIN SR in a tightly closed container.
- 851 • Keep WELLBUTRIN SR out of the reach of children.

852

853 This summary provides important information about WELLBUTRIN SR. This summary cannot
854 replace the more detailed information that you need from your doctor. If you have any questions or
855 concerns about either WELLBUTRIN SR or depression, talk to your doctor or other health care
856 professional.

857



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Russell Katz
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