

PRESCRIBING INFORMATION

1  
2 **WELLBUTRIN<sup>®</sup>**  
3 **(bupropion hydrochloride)**  
4 **Tablets**  
5

6 **WARNING**

7 **Suicidality and Antidepressant Drugs**

8 ***Use in Treating Psychiatric Disorders:*** Antidepressants increased the risk compared to  
9 placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults  
10 in short-term studies of major depressive disorder (MDD) and other psychiatric disorders.

11 Anyone considering the use of WELLBUTRIN or any other antidepressant in a child, adolescent,  
12 or young adult must balance this risk with the clinical need. Short-term studies did not show an  
13 increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age  
14 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and  
15 older. Depression and certain other psychiatric disorders are themselves associated with  
16 increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy  
17 should be monitored appropriately and observed closely for clinical worsening, suicidality, or  
18 unusual changes in behavior. Families and caregivers should be advised of the need for close  
19 observation and communication with the prescriber. WELLBUTRIN is not approved for use in  
20 pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk in Treating  
21 Psychiatric Disorders, PRECAUTIONS: Information for Patients, and PRECAUTIONS:  
22 Pediatric Use.)

23 ***Use in Smoking Cessation Treatment:*** WELLBUTRIN<sup>®</sup>, WELLBUTRIN SR<sup>®</sup>, and  
24 WELLBUTRIN XL<sup>®</sup> are not approved for smoking cessation treatment, but bupropion under the  
25 name ZYBAN<sup>®</sup> is approved for this use. Serious neuropsychiatric events, including but not  
26 limited to depression, suicidal ideation, suicide attempt, and completed suicide have been  
27 reported in patients taking bupropion for smoking cessation. Some cases may have been  
28 complicated by the symptoms of nicotine withdrawal in patients who stopped smoking.  
29 Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including  
30 suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without  
31 medication. However, some of these symptoms have occurred in patients taking bupropion who  
32 continued to smoke.

33 All patients being treated with bupropion for smoking cessation treatment should be observed  
34 for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed  
35 mood, and suicide-related events, including ideation, behavior, and attempted suicide. These  
36 symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have  
37 been reported in some patients attempting to quit smoking while taking ZYBAN in the  
38 postmarketing experience. When symptoms were reported, most were during treatment with  
39 ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have  
40 occurred in patients with and without pre-existing psychiatric disease; some have experienced

41 worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as  
42 schizophrenia, bipolar disorder, and major depressive disorder did not participate in the  
43 premarketing studies of ZYBAN.

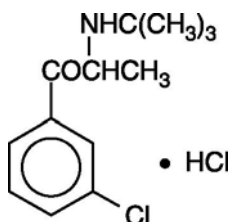
44 **Advise patients and caregivers that the patient using bupropion for smoking cessation**  
45 **should stop taking bupropion and contact a healthcare provider immediately if agitation,**  
46 **hostility, depressed mood, or changes in thinking or behavior that are not typical for the**  
47 **patient are observed, or if the patient develops suicidal ideation or suicidal behavior.** In  
48 many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was  
49 reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and  
50 supportive care should be provided until symptoms resolve.

51 The risks of using bupropion for smoking cessation should be weighed against the benefits of  
52 its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking  
53 for as long as 6 months compared to treatment with placebo. The health benefits of quitting  
54 smoking are immediate and substantial. (See WARNINGS: Neuropsychiatric Symptoms and  
55 Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)

## 56 DESCRIPTION

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

65



66

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

74 **CLINICAL PHARMACOLOGY**

75 **Pharmacodynamics:** The neurochemical mechanism of the antidepressant effect of  
76 bupropion is not known. Bupropion is a relatively weak inhibitor of the neuronal uptake of  
77 norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of  
78 serotonin.

79 Bupropion produces dose-related central nervous system (CNS) stimulant effects in animals,  
80 as evidenced by increased locomotor activity, increased rates of responding in various  
81 schedule-controlled operant behavior tasks, and, at high doses, induction of mild stereotyped  
82 behavior.

83 Bupropion causes convulsions in rodents and dogs at doses approximately tenfold the dose  
84 recommended as the human antidepressant dose.

85 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacological activity and  
86 pharmacokinetics of the individual enantiomers have not been studied. In humans, following oral  
87 administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved  
88 within 2 hours, followed by a biphasic decline. The terminal phase has a mean half-life of  
89 14 hours, with a range of 8 to 24 hours. The distribution phase has a mean half-life of 3 to  
90 4 hours. The mean elimination half-life ( $\pm$ SD) of bupropion after chronic dosing is 21 ( $\pm$ 9)  
91 hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma  
92 bupropion concentrations are dose-proportional following single doses of 100 to 250 mg;  
93 however, it is not known if the proportionality between dose and plasma level is maintained in  
94 chronic use.

95 **Absorption:** The absolute bioavailability of WELLBUTRIN in humans has not been  
96 determined because an intravenous formulation for human use is not available. However, it  
97 appears likely that only a small proportion of any orally administered dose reaches the systemic  
98 circulation intact.

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

103 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
104 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
105 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
106 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
107 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
108 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
109 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-  
110 chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and  
111 toxicity of the metabolites relative to bupropion have not been fully characterized. However, it  
112 has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is  
113 one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-

114 fold less potent than bupropion. This may be of clinical importance because their plasma  
115 concentrations are as high or higher than those of bupropion.

116 Because bupropion is extensively metabolized, there is the potential for drug-drug  
117 interactions, particularly with those agents that are metabolized by or which inhibit/induce the  
118 cytochrome P450IIB6 (CYP2B6) isoenzyme, such as ritonavir. In a healthy volunteer study,  
119 ritonavir at a dose of 100 mg twice daily reduced the AUC and  $C_{max}$  of bupropion by 22% and  
120 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the  
121 threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

122 In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the  
123 AUC and the  $C_{max}$  of bupropion by 66% and 62%, respectively. The exposure of the  
124 hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by  
125 50%, and the erythrohydrobupropion decreased by 68%.

126 In another healthy volunteer study, KALETRA<sup>®\*</sup> (lopinavir 400 mg/ritonavir 100 mg twice  
127 daily) decreased bupropion AUC and  $C_{max}$  by 57%. The AUC and  $C_{max}$  of hydroxybupropion  
128 were decreased by 50% and 31%, respectively (see PRECAUTIONS: Drug Interactions).

129 Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the  
130 potential for drug-drug interactions when bupropion is coadministered with drugs metabolized  
131 by this isoenzyme (see PRECAUTIONS: Drug Interactions).

132 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur  
133 approximately 3 hours after administration of WELLBUTRIN. Peak plasma concentrations of  
134 hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state.  
135 The elimination half-life of hydroxybupropion is approximately 20 ( $\pm$ 5) hours, and its AUC at  
136 steady state is about 17 times that of bupropion. The times to peak concentrations for the  
137 erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the  
138 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 ( $\pm$ 10) and  
139 37 ( $\pm$ 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,  
140 respectively.

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

143 **Elimination:** Following oral administration of 200 mg of <sup>14</sup>C-bupropion in humans, 87% and  
144 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the  
145 fraction of the oral dose of WELLBUTRIN excreted unchanged was only 0.5%, a finding  
146 consistent with the extensive metabolism of bupropion.

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

153 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was  
154 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in  
155 patients with mild-to-severe cirrhosis. The first study showed that the half-life of  
156 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in  
157 8 healthy volunteers ( $32 \pm 14$  hours versus  $21 \pm 5$  hours, respectively). Although not statistically  
158 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be  
159 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life  
160 for bupropion and the other metabolites in the 2 patient groups were minimal.

161 The second study showed that there were no statistically significant differences in the  
162 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild-to-moderate  
163 hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in  
164 some of the pharmacokinetic parameters for bupropion (AUC,  $C_{\max}$ , and  $T_{\max}$ ) and its active  
165 metabolites ( $t_{1/2}$ ) in patients with mild-to-moderate hepatic cirrhosis. In addition, in patients with  
166 severe hepatic cirrhosis, the bupropion  $C_{\max}$  and AUC were substantially increased (mean  
167 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to  
168 values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients  
169 with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite  
170 hydroxybupropion, the mean  $C_{\max}$  was approximately 69% lower. For the combined amino-  
171 alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean  $C_{\max}$  was  
172 approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion  
173 and about 2½-fold for threo/erythrohydrobupropion. The median  $T_{\max}$  was observed 19 hours  
174 later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean  
175 half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold,  
176 respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see  
177 WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

178 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
179 renal impairment. An inter-study comparison between normal subjects and patients with end-  
180 stage renal failure demonstrated that the parent drug  $C_{\max}$  and AUC values were comparable in  
181 the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-  
182 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. A second  
183 study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR  
184  $30.9 \pm 10.8$  mL/min) showed that exposure to a single 150-mg dose of sustained-release  
185 bupropion was approximately 2-fold higher in patients with impaired renal function while levels  
186 of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar  
187 in the 2 groups. The elimination of bupropion and/or the major metabolites of bupropion may be  
188 reduced by impaired renal function (see PRECAUTIONS: Renal Impairment).

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

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

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

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

## 210 **INDICATIONS AND USAGE**

211 WELLBUTRIN is indicated for the treatment of major depressive disorder. A physician  
212 considering WELLBUTRIN for the management of a patient's first episode of depression should  
213 be aware that the drug may cause generalized seizures in a dose-dependent manner with an  
214 approximate incidence of 0.4% (4/1,000). This incidence of seizures may exceed that of other  
215 marketed antidepressants by as much as 4-fold. This relative risk is only an approximate estimate  
216 because no direct comparative studies have been conducted (see WARNINGS).

217 The efficacy of WELLBUTRIN has been established in 3 placebo-controlled trials, including  
218 2 of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks'  
219 duration in depressed outpatients. The depressive disorder of the patients studied corresponds  
220 most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

221 Major Depression implies a prominent and relatively persistent depressed or dysphoric mood  
222 that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should  
223 include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor  
224 agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased  
225 fatigability, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and  
226 suicidal ideation or attempts.

227 Effectiveness of WELLBUTRIN in long-term use, that is, for more than 6 weeks, has not  
228 been systematically evaluated in controlled trials. Therefore, the physician who elects to use  
229 WELLBUTRIN for extended periods should periodically reevaluate the long-term usefulness of  
230 the drug for the individual patient.

231 **CONTRAINDICATIONS**

232 WELLBUTRIN is contraindicated in patients with a seizure disorder.

233 WELLBUTRIN is contraindicated in patients treated with ZYBAN<sup>®</sup> (bupropion  
234 hydrochloride) Sustained-Release Tablets; WELLBUTRIN SR<sup>®</sup> (bupropion hydrochloride), the  
235 sustained-release formulation; WELLBUTRIN XL<sup>®</sup> (bupropion hydrochloride), the extended-  
236 release formulation; or any other medications that contain bupropion because the incidence of  
237 seizure is dose dependent.

238 WELLBUTRIN is contraindicated in patients with a current or prior diagnosis of bulimia or  
239 anorexia nervosa because of a higher incidence of seizures noted in such patients treated with  
240 WELLBUTRIN.

241 WELLBUTRIN is contraindicated in patients undergoing abrupt discontinuation of alcohol or  
242 sedatives (including benzodiazepines).

243 The concurrent administration of WELLBUTRIN and a monoamine oxidase (MAO) inhibitor  
244 is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor  
245 and initiation of treatment with WELLBUTRIN.

246 WELLBUTRIN is contraindicated in patients who have shown an allergic response to  
247 bupropion or the other ingredients that make up WELLBUTRIN.

248 **WARNINGS**

249 **Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders:** Patients  
250 with major depressive disorder (MDD), both adult and pediatric, may experience worsening of  
251 their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual  
252 changes in behavior, whether or not they are taking antidepressant medications, and this risk may  
253 persist until significant remission occurs. Suicide is a known risk of depression and certain other  
254 psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.  
255 There has been a long-standing concern, however, that antidepressants may have a role in  
256 inducing worsening of depression and the emergence of suicidality in certain patients during the  
257 early phases of treatment. Pooled analyses of short-term placebo-controlled trials of  
258 antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal  
259 thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with  
260 major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not  
261 show an increase in the risk of suicidality with antidepressants compared to placebo in adults  
262 beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65  
263 and older.

264 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
265 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24  
266 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of  
267 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of  
268 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000  
269 patients. There was considerable variation in risk of suicidality among drugs, but a tendency

270 toward an increase in the younger patients for almost all drugs studied. There were differences in  
271 absolute risk of suicidality across the different indications, with the highest incidence in MDD.  
272 The risk differences (drug vs placebo), however, were relatively stable within age strata and  
273 across indications. These risk differences (drug-placebo difference in the number of cases of  
274 suicidality per 1,000 patients treated) are provided in Table 1.

275  
276

**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

277

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

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

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

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

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

299 **Families and caregivers of patients being treated with antidepressants for major**  
300 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**  
301 **alerted about the need to monitor patients for the emergence of agitation, irritability,**

302 **unusual changes in behavior, and the other symptoms described above, as well as the**  
303 **emergence of suicidality, and to report such symptoms immediately to healthcare**  
304 **providers. Such monitoring should include daily observation by families and caregivers.**

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

307 **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment:**

308 WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL are not approved for smoking  
309 cessation treatment, but bupropion under the name ZYBAN is approved for this use. Serious  
310 neuropsychiatric symptoms have been reported in patients taking bupropion for smoking  
311 cessation (see **BOXED WARNING, ADVERSE REACTIONS**). **These have included**  
312 **changes in mood (including depression and mania), psychosis, hallucinations, paranoia,**  
313 **delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as**  
314 **suicidal ideation, suicide attempt, and completed suicide.** Some reported cases may have been  
315 complicated by the symptoms of nicotine withdrawal in patients who stopped smoking.  
316 Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including  
317 suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without  
318 medication. However, some of these symptoms have occurred in patients taking bupropion who  
319 continued to smoke. When symptoms were reported, most were during bupropion treatment, but  
320 some were following discontinuation of bupropion therapy.

321 These events have occurred in patients with and without pre-existing psychiatric disease;  
322 some have experienced worsening of their psychiatric illnesses. All patients being treated with  
323 bupropion as part of smoking cessation treatment should be observed for neuropsychiatric  
324 symptoms or worsening of pre-existing psychiatric illness.

325 Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major  
326 depressive disorder did not participate in the pre-marketing studies of ZYBAN.

327 **Advise patients and caregivers that the patient using bupropion for smoking cessation**  
328 **should stop taking bupropion and contact a healthcare provider immediately if agitation,**  
329 **depressed mood, or changes in behavior or thinking that are not typical for the patient are**  
330 **observed, or if the patient develops suicidal ideation or suicidal behavior. In many**  
331 **postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was**  
332 **reported, although in some cases the symptoms persisted, therefore, ongoing monitoring**  
333 **and supportive care should be provided until symptoms resolve.**

334 The risks of using bupropion for smoking cessation should be weighed against the benefits of  
335 its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking  
336 for as long as six months compared to treatment with placebo. The health benefits of quitting  
337 smoking are immediate and substantial.

338 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial  
339 presentation of bipolar disorder. It is generally believed (though not established in controlled  
340 trials) that treating such an episode with an antidepressant alone may increase the likelihood of  
341 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the

342 symptoms described above represent such a conversion is unknown. However, prior to initiating  
343 treatment with an antidepressant, patients with depressive symptoms should be adequately  
344 screened to determine if they are at risk for bipolar disorder; such screening should include a  
345 detailed psychiatric history, including a family history of suicide, bipolar disorder, and  
346 depression. It should be noted that WELLBUTRIN is not approved for use in treating bipolar  
347 depression.

348 **Bupropion-Containing Products:** Patients should be made aware that WELLBUTRIN  
349 contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation  
350 treatment, and that WELLBUTRIN should not be used in combination with ZYBAN, or any  
351 other medications that contain bupropion, such as WELLBUTRIN SR (bupropion  
352 hydrochloride), the sustained-release formulation or WELLBUTRIN XL (bupropion  
353 hydrochloride), the extended-release formulation.

354

355 **Seizures:** Bupropion is associated with seizures in approximately 0.4% (4/1,000) of  
356 patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of  
357 other marketed antidepressants by as much as 4-fold. This relative risk is only an  
358 approximate estimate because no direct comparative studies have been conducted. The  
359 estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and  
360 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third  
361 the maximum recommended daily dose (450 mg). Given the wide variability among  
362 individuals and their capacity to metabolize and eliminate drugs this disproportionate  
363 increase in seizure incidence with dose incrementation calls for caution in dosing.

364 During the initial development, 25 among approximately 2,400 patients treated with  
365 WELLBUTRIN experienced seizures. At the time of seizure, 7 patients were receiving daily  
366 doses of 450 mg or below for an incidence of 0.33% (3/1,000) within the recommended dose  
367 range. Twelve patients experienced seizures at 600 mg/day (2.3% incidence); 6 additional  
368 patients had seizures at daily doses between 600 and 900 mg (2.8% incidence).

369 A separate, prospective study was conducted to determine the incidence of seizure  
370 during an 8-week treatment exposure in approximately 3,200 additional patients who  
371 received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond  
372 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment  
373 period and 5 seizures were reported in patients continuing treatment beyond 8 weeks,  
374 resulting in a total seizure incidence of 0.4%.

375 The risk of seizure appears to be strongly associated with dose. Sudden and large  
376 increments in dose may contribute to increased risk. While many seizures occurred early in  
377 the course of treatment, some seizures did occur after several weeks at fixed dose.  
378 WELLBUTRIN should be discontinued and not restarted in patients who experience a  
379 seizure while on treatment.

380       The risk of seizure is also related to patient factors, clinical situations, and concomitant  
381 medications, which must be considered in selection of patients for therapy with  
382 WELLBUTRIN.

- 383       • **Patient factors:** Predisposing factors that may increase the risk of seizure with  
384 bupropion use include history of head trauma or prior seizure, central nervous system  
385 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications  
386 that lower seizure threshold.
- 387       • **Clinical situations:** Circumstances associated with an increased seizure risk include,  
388 among others, excessive use of alcohol or sedatives (including benzodiazepines);  
389 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and  
390 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 391       • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,  
392 theophylline, systemic steroids) are known to lower seizure threshold.

393       **Recommendations for Reducing the Risk of Seizure:** Retrospective analysis of  
394 clinical experience gained during the development of WELLBUTRIN suggests that the risk  
395 of seizure may be minimized if

- 396       • the total daily dose of WELLBUTRIN does *not* exceed 450 mg,
- 397       • the daily dose is administered 3 times daily, with each single dose *not* to exceed 150 mg  
398 to avoid high peak concentrations of bupropion and/or its metabolites, and
- 399       • the rate of incrementation of dose is very gradual.

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

404       **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients  
405 with severe hepatic cirrhosis. In these patients a reduced dose and/or frequency is required,  
406 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is  
407 likely to occur in such patients to a greater extent than usual. The dose should not exceed  
408 75 mg once a day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS,  
409 and DOSAGE AND ADMINISTRATION).

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

## 414       **PRECAUTIONS**

415       **General: Agitation and Insomnia:** A substantial proportion of patients treated with  
416 WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and  
417 insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were  
418 sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In

419 approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of  
420 treatment with WELLBUTRIN.

421 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Depressed  
422 patients treated with WELLBUTRIN have been reported to show a variety of neuropsychiatric  
423 signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance,  
424 paranoia, and confusion. Because of the uncontrolled nature of many studies, it is impossible to  
425 provide a precise estimate of the extent of risk imposed by treatment with WELLBUTRIN. In  
426 several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of  
427 treatment.

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

431 **Altered Appetite and Weight:** A weight loss of greater than 5 lbs occurred in 28% of  
432 patients receiving WELLBUTRIN. This incidence is approximately double that seen in  
433 comparable patients treated with tricyclics or placebo. Furthermore, while 35% of patients  
434 receiving tricyclic antidepressants gained weight, only 9.4% of patients treated with  
435 WELLBUTRIN did. Consequently, if weight loss is a major presenting sign of a patient's  
436 depressive illness, the anorectic and/or weight reducing potential of WELLBUTRIN should be  
437 considered.

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

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

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

452 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN®  
453 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-  
454 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher  
455 incidence of treatment-emergent hypertension in patients treated with the combination of  
456 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the  
457 combination of sustained-release bupropion and NTS had treatment-emergent hypertension  
458 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,

459 and placebo, respectively. The majority of these patients had evidence of preexisting  
460 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1  
461 patient (0.4%) treated with NTS had study medication discontinued due to hypertension  
462 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure  
463 is recommended in patients who receive the combination of bupropion and nicotine replacement.

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

472 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients with  
473 severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required.  
474 WELLBUTRIN should be used with caution in patients with hepatic impairment (including  
475 mild-to-moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in  
476 patients with mild-to-moderate hepatic cirrhosis.

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

480 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
481 patients with renal impairment. An inter-study comparison between normal subjects and patients  
482 with end-stage renal failure demonstrated that the parent drug  $C_{max}$  and AUC values were  
483 comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
484 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage  
485 renal failure. A second study, comparing normal subjects and patients with moderate-to-severe  
486 renal impairment (GFR  $30.9 \pm 10.8$  mL/min) showed that exposure to a single 150-mg dose of  
487 sustained-release bupropion was approximately 2-fold higher in patients with impaired renal  
488 function while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined)  
489 metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to  
490 active metabolites, which are further metabolized and subsequently excreted by the kidneys.  
491 WELLBUTRIN should be used with caution in patients with renal impairment and a reduced  
492 frequency and/or dose should be considered as bupropion and the metabolites of bupropion may  
493 accumulate in such patients to a greater extent than usual. The patient should be closely  
494 monitored for possible adverse effects that could indicate high drug or metabolite levels.

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

499 Thoughts or Actions,” “Quitting Smoking, Quit-Smoking Medication, Changes in Thinking and  
500 Behavior, Depression, and Suicidal Thoughts or Actions,” and “What Other Important  
501 Information Should I Know About WELLBUTRIN ?” is available for WELLBUTRIN. The  
502 prescriber or health professional should instruct patients, their families, and their caregivers to  
503 read the Medication Guide and should assist them in understanding its contents. Patients should  
504 be given the opportunity to discuss the contents of the Medication Guide and to obtain answers  
505 to any questions they may have. The complete text of the Medication Guide is reprinted at the  
506 end of this document.

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

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

520 **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation**

521 **Treatment:** Although WELLBUTRIN is not indicated for smoking cessation treatment, it  
522 contains the same active ingredient as ZYBAN which is approved for this use. Patients should be  
523 informed that quitting smoking, with or without ZYBAN, may be associated with nicotine  
524 withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing  
525 psychiatric illness. Furthermore, some patients have experienced changes in mood (including  
526 depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation  
527 aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed  
528 suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation,  
529 hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if  
530 patients develop suicidal ideation or behavior, they should be urged to report these symptoms to  
531 their healthcare provider immediately.

532 **Bupropion-Containing Products:** Patients should be made aware that WELLBUTRIN  
533 contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation, and  
534 that WELLBUTRIN should not be used in combination with ZYBAN or any other medications  
535 that contain bupropion hydrochloride (such as WELLBUTRIN SR, the sustained-release  
536 formulation and WELLBUTRIN XL, the extended-release formulation).

537 Patients should be instructed to take WELLBUTRIN in equally divided doses 3 or 4 times a  
538 day to minimize the risk of seizure.

539 Patients should be told that WELLBUTRIN should be discontinued and not restarted if they  
540 experience a seizure while on treatment.

541 Patients should be told that any CNS-active drug like WELLBUTRIN may impair their ability  
542 to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are  
543 reasonably certain that WELLBUTRIN does not adversely affect their performance, they should  
544 refrain from driving an automobile or operating complex, hazardous machinery.

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

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

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

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

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

558 Because bupropion is extensively metabolized, the coadministration of other drugs may affect  
559 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to  
560 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
561 interaction between WELLBUTRIN and drugs that are substrates of or inhibitors/inducers of the  
562 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and  
563 clopidogrel). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and  
564 fluvoxamine as well as nelfinavir and efavirenz inhibit the hydroxylation of bupropion. No  
565 clinical studies have been performed to evaluate this finding. The threohydrobupropion  
566 metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes.  
567 The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion  
568 and its active metabolites were studied in 24 healthy young male volunteers. Following oral  
569 administration of two 150-mg sustained-release tablets with and without 800 mg of cimetidine,  
570 the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were  
571 16% and 32% increases in the AUC and  $C_{max}$ , respectively, of the combined moieties of  
572 threohydrobupropion and erythrohydrobupropion.

573 In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice  
574 daily) or ritonavir 100 mg plus lopinavir 400 mg (KALETRA) twice daily reduced the exposure  
575 of bupropion and its major metabolites in a dose dependent manner by approximately 20% to  
576 80%. This effect is thought to be due to the induction of bupropion metabolism. Patients  
577 receiving ritonavir may need increased doses of bupropion, but the maximum recommended  
578 dose of bupropion should not be exceeded (see CLINICAL PHARMACOLOGY: Metabolism).

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

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

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

588 **Drugs Metabolized by Cytochrome P450IID6 (CYP2D6):** Many drugs, including most  
589 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are  
590 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this  
591 isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro.  
592 In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the  
593 CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single  
594 dose of 50 mg desipramine increased the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of  
595 approximately 2-, 5- and 2-fold, respectively. The effect was present for at least 7 days after the  
596 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6  
597 has not been formally studied.

598 Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6  
599 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,  
600 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),  
601 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),  
602 should be approached with caution and should be initiated at the lower end of the dose range of  
603 the concomitant medication. If bupropion is added to the treatment regimen of a patient already  
604 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original  
605 medication should be considered, particularly for those concomitant medications with a narrow  
606 therapeutic index.

607 Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion  
608 increased the  $C_{max}$  and AUC of citalopram by 30% and 40%, respectively. Citalopram did not  
609 affect the pharmacokinetics of bupropion and its 3 metabolites.

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

612 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
613 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
614 Administration of WELLBUTRIN to patients receiving either levodopa or amantadine  
615 concurrently should be undertaken with caution, using small initial doses and small gradual dose  
616 increases.

617 **Drugs that Lower Seizure Threshold:** Concurrent administration of WELLBUTRIN and  
618 agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that

619 lower seizure threshold should be undertaken only with extreme caution (see WARNINGS).  
620 Low initial dosing and small gradual dose increases should be employed.

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

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

626 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies  
627 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat  
628 study there was an increase in nodular proliferative lesions of the liver at doses of 100 to  
629 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be  
630 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen  
631 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in  
632 either study.

633 Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in  
634 some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not  
635 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance  
636 of these results in estimating the risk of human exposure to therapeutic doses is unknown.

637 A fertility study was performed in rats; no evidence of impairment of fertility was  
638 encountered at oral doses up to 300 mg/kg/day.

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

646 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
647 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
648 there were no apparent adverse effects on offspring development.

649 One study has been conducted in pregnant women. This retrospective, managed-care database  
650 study assessed the risk of congenital malformations overall and cardiovascular malformations  
651 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
652 malformations following exposure to other antidepressants in the first trimester and bupropion  
653 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
654 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
655 showed no greater risk for congenital malformations overall or cardiovascular malformations  
656 specifically, following first trimester bupropion exposure compared to exposure to all other  
657 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of

658 this study have not been corroborated. WELLBUTRIN should be used during pregnancy only if  
659 the potential benefit justifies the potential risk to the fetus.

660 **Labor and Delivery:** The effect of WELLBUTRIN on labor and delivery in humans is  
661 unknown.

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

666 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established  
667 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk in Treating  
668 Psychiatric Disorders). Anyone considering the use of WELLBUTRIN in a child or adolescent  
669 must balance the potential risks with the clinical need.

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

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

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

## 687 688 **ADVERSE REACTIONS**

689 (See also WARNINGS and PRECAUTIONS.)

690 Adverse events commonly encountered in patients treated with WELLBUTRIN are agitation,  
691 dry mouth, insomnia, headache/migraine, nausea/vomiting, constipation, and tremor.

692 Adverse events were sufficiently troublesome to cause discontinuation of treatment with  
693 WELLBUTRIN in approximately 10% of the 2,400 patients and volunteers who participated in  
694 clinical trials during the product's initial development. The more common events causing  
695 discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and  
696 abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and  
697 vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep

698 disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note,  
699 however, that many of these events occurred at doses that exceed the recommended daily dose.

700 Accurate estimates of the incidence of adverse events associated with the use of any drug are  
701 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician  
702 judgments, etc. Consequently, Table 2 is presented solely to indicate the relative frequency of  
703 adverse events reported in representative controlled clinical studies conducted to evaluate the  
704 safety and efficacy of WELLBUTRIN under relatively similar conditions of daily dosage (300 to  
705 600 mg), setting, and duration (3 to 4 weeks). The figures cited cannot be used to predict  
706 precisely the incidence of untoward events in the course of usual medical practice where patient  
707 characteristics and other factors must differ from those which prevailed in the clinical trials.  
708 These incidence figures also cannot be compared with those obtained from other clinical studies  
709 involving related drug products as each group of drug trials is conducted under a different set of  
710 conditions.

711 Finally, it is important to emphasize that the tabulation does not reflect the relative severity  
712 and/or clinical importance of the events. A better perspective on the serious adverse events  
713 associated with the use of WELLBUTRIN is provided in WARNINGS and PRECAUTIONS.

714

715 **Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
716 **Clinical Trials<sup>a</sup> (Percent of Patients Reporting)**

Adverse Experience	WELLBUTRIN Patients (n = 323)	Placebo Patients (n = 185)
Cardiovascular		
Cardiac arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
Dermatologic		
Pruritus	2.2	0.0
Rash	8.0	6.5
Gastrointestinal		
Anorexia	18.3	18.4
Appetite increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/vomiting	22.9	18.9

Weight gain	13.6	22.7
Weight loss	23.2	23.2
Genitourinary		
Impotence	3.4	3.1
Menstrual complaints	4.7	1.1
Urinary frequency	2.5	2.2
Urinary retention	1.9	2.2
Musculoskeletal		
Arthritis	3.1	2.7
Neurological		
Akathisia	1.5	1.1
Akinesia/bradykinesia	8.0	8.6
Cutaneous temperature disturbance	1.9	1.6
Dry mouth	27.6	18.4
Excessive sweating	22.3	14.6
Headache/migraine	25.7	22.2
Impaired sleep quality	4.0	1.6
Increased salivary flow	3.4	3.8
Insomnia	18.6	15.7
Muscle spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory disturbance	4.0	3.2
Tremor	21.1	7.6
Neuropsychiatric		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased libido	3.1	1.6
Delusions	1.2	1.1
Disturbed concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
Nonspecific		
Fatigue	5.0	8.6
Fever/chills	1.2	0.5

Respiratory Upper respiratory complaints	5.0	11.4
Special Senses		
Auditory disturbance	5.3	3.2
Blurred vision	14.6	10.3
Gustatory disturbance	3.1	1.1

717 <sup>a</sup> Events reported by at least 1% of patients receiving WELLBUTRIN are included.

718

719 **Other Events Observed During the Development of WELLBUTRIN:** The conditions  
720 and duration of exposure to WELLBUTRIN varied greatly, and a substantial proportion of the  
721 experience was gained in open and uncontrolled clinical settings. During this experience,  
722 numerous adverse events were reported; however, without appropriate controls, it is impossible  
723 to determine with certainty which events were or were not caused by WELLBUTRIN. The  
724 following enumeration is organized by organ system and describes events in terms of their  
725 relative frequency of reporting in the data base. Events of major clinical importance are also  
726 described in WARNINGS and PRECAUTIONS.

727 The following definitions of frequency are used: Frequent adverse events are defined as those  
728 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
729 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

733 **Dermatologic:** Frequent were nonspecific rashes; infrequent were alopecia and dry skin;  
734 rare were change in hair color, hirsutism, and acne.

735 **Endocrine:** Infrequent was gynecomastia; rare were glycosuria and hormone level change.

736 **Gastrointestinal:** Infrequent were dysphagia, thirst disturbance, and liver damage/jaundice;  
737 rare were rectal complaints, colitis, gastrointestinal bleeding, intestinal perforation, and stomach  
738 ulcer.

739 **Genitourinary:** Frequent was nocturia; infrequent were vaginal irritation, testicular swelling,  
740 urinary tract infection, painful erection, and retarded ejaculation; rare were dysuria, enuresis,  
741 urinary incontinence, menopause, ovarian disorder, pelvic infection, cystitis, dyspareunia, and  
742 painful ejaculation.

743 **Hematologic/Oncologic:** Rare were lymphadenopathy, anemia, and pancytopenia.

744 **Musculoskeletal:** Rare was musculoskeletal chest pain.

745 **Neurological:** (see WARNINGS) Frequent were ataxia/incoordination, seizure, myoclonus,  
746 dyskinesia, and dystonia; infrequent were mydriasis, vertigo, and dysarthria; rare were  
747 electroencephalogram (EEG) abnormality, abnormal neurological exam, impaired attention,  
748 sciatica, and aphasia.

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

753 **Oral Complaints:** Frequent was stomatitis; infrequent were toothache, bruxism, gum  
754 irritation, and oral edema; rare was glossitis.

755 **Respiratory:** Infrequent were bronchitis and shortness of breath/dyspnea; rare were  
756 epistaxis, rate or rhythm disorder, pneumonia, and pulmonary embolism.

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

758 **Nonspecific:** Frequent were flu-like symptoms; infrequent was nonspecific pain; rare were  
759 body odor, surgically related pain, infection, medication reaction, and overdose.

760 **Postintroduction Reports:** Voluntary reports of adverse events temporally associated with  
761 bupropion that have been received since market introduction and which may have no causal  
762 relationship with the drug include the following:

763 **Body (General):** arthralgia, myalgia, and fever with rash and other symptoms suggestive of  
764 delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

765 **Cardiovascular:** hypertension (in some cases severe, see PRECAUTIONS), orthostatic  
766 hypotension, third degree heart block

767 **Endocrine:** syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia,  
768 hypoglycemia

769 **Gastrointestinal:** esophagitis, hepatitis, liver damage

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

773 **Musculoskeletal:** arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis, muscle  
774 weakness

775 **Nervous:** aggression, coma, completed suicide, delirium, dream abnormalities, paranoid  
776 ideation, paresthesia, restlessness, suicide attempt, unmasking of tardive dyskinesia

777 **Skin and Appendages:** Stevens-Johnson syndrome, angioedema, exfoliative dermatitis,  
778 urticaria

779 **Special Senses:** tinnitus, increased intraocular pressure

## 780 **DRUG ABUSE AND DEPENDENCE**

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

784 In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of  
785 WELLBUTRIN produced mild amphetamine-like activity as compared to placebo on the  
786 Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a

787 score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These  
788 scales measure general feelings of euphoria and drug desirability.

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

794 **Animals:** Studies in rodents have shown that bupropion exhibits some pharmacologic actions  
795 common to psychostimulants including increases in locomotor activity and the production of a  
796 mild stereotyped behavior and increases in rates of responding in several schedule-controlled  
797 behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between  
798 bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to  
799 self-administer bupropion intravenously.

## 800 **OVERDOSAGE**

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

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

811 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
812 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
813 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
814 Induction of emesis is not recommended.

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

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

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

826 **DOSAGE AND ADMINISTRATION**

827 **General Dosing Considerations:** It is particularly important to administer WELLBUTRIN  
828 in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose  
829 should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important  
830 if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are  
831 to be minimized. If necessary, these effects may be managed by temporary reduction of dose or  
832 the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative  
833 hypnotic usually is not required beyond the first week of treatment. Insomnia may also be  
834 minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation  
835 should be stopped.

836 No single dose of WELLBUTRIN should exceed 150 mg. WELLBUTRIN should be  
837 administered 3 times daily, preferably with at least 6 hours between successive doses.

838 **Usual Dosage for Adults:** The usual adult dose is 300 mg/day, given 3 times daily. Dosing  
839 should begin at 200 mg/day, given as 100 mg twice daily. Based on clinical response, this dose  
840 may be increased to 300 mg/day, given as 100 mg 3 times daily, no sooner than 3 days after  
841 beginning therapy (see Table 3).

842

843 **Table 3. Dosing Regimen**

Treatment Day	Total Daily Dose	Tablet Strength	Number of Tablets		
			Morning	Midday	Evening
1	200 mg	100 mg	1	0	1
4	300 mg	100 mg	1	1	1

844

845 **Increasing the Dosage Above 300 mg/Day:** As with other antidepressants, the full  
846 antidepressant effect of WELLBUTRIN may not be evident until 4 weeks of treatment or longer.  
847 An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than  
848 150 mg each, may be considered for patients in whom no clinical improvement is noted after  
849 several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished  
850 using the 75- or 100-mg tablets. The 100-mg tablet must be administered 4 times daily with at  
851 least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single  
852 dose. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate  
853 response after an appropriate period of treatment at 450 mg/day.

854 **Maintenance Treatment:** The lowest dose that maintains remission is recommended.  
855 Although it is not known how long the patient should remain on WELLBUTRIN, it is generally  
856 recognized that acute episodes of depression require several months or longer of antidepressant  
857 drug treatment.

858 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN  
859 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should  
860 not exceed 75 mg once a day in these patients. WELLBUTRIN should be used with caution in  
861 patients with hepatic impairment (including mild-to-moderate hepatic cirrhosis) and a reduced

862 frequency and/or dose should be considered in patients with mild-to-moderate hepatic cirrhosis  
863 (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

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

## 867 **HOW SUPPLIED**

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

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

872 **Store at 15° to 25°C (59° to 77°F). Protect from light and moisture.**

873

## 874 **MEDICATION GUIDE**

### 875 **WELLBUTRIN<sup>®</sup> (WELL byu-trin)** 876 **(bupropion hydrochloride) Tablets**

877

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

882

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

888

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

891

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

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

897

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

- 900 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**  
901 **teenagers, and young adults within the first few months of treatment.**
- 902 **2. Depression and other serious mental illnesses are the most important causes of suicidal**  
903 **thoughts and actions. Some people may have a particularly high risk of having suicidal**  
904 **thoughts or actions.** These include people who have (or have a family history of) bipolar  
905 illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 906 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**  
907 **family member?**
- 908 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,  
909 thoughts, or feelings. This is very important when an antidepressant medicine is started or  
910 when the dose is changed.
  - 911 • Call the healthcare provider right away to report new or sudden changes in mood,  
912 behavior, thoughts, or feelings.
  - 913 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare  
914 provider between visits as needed, especially if you have concerns about symptoms.
- 915

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

918

- 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

919

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

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

- 932 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**  
933 **children.** Talk to your child’s healthcare provider for more information.

934  
935 WELLBUTRIN has not been studied in children under the age of 18 and is not approved for use  
936 in children and teenagers.

937  
938 **Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior,**  
939 **Depression, and Suicidal Thoughts or Actions**

940  
941 This section of the Medication Guide is only about the risk of changes in thinking and behavior,  
942 depression and suicidal thoughts or actions with drugs used to quit smoking.

943  
944 Although WELLBUTRIN is not a treatment for quitting smoking, it contains the same active  
945 ingredient (bupropion hydrochloride) as ZYBAN<sup>®</sup> which is used to help patients quit smoking.

946  
947 Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or  
948 actions while taking bupropion to help them quit smoking. These symptoms can develop during  
949 treatment with bupropion or after stopping treatment with bupropion.

950  
951 If you, your family member, or your caregiver notice agitation, hostility, depression, or changes  
952 in thinking or behavior that are not typical for you, or you have any of the following symptoms,  
953 stop taking bupropion and call your healthcare provider right away:

- 954
- thoughts about suicide or dying
  - attempts to commit suicide
  - new or worse depression
  - new or worse anxiety
  - panic attacks
  - feeling very agitated or restless
  - acting aggressive, being angry, or violent
  - acting on dangerous impulses
  - an extreme increase in activity and talking (mania)
  - abnormal thoughts or sensations
  - seeing or hearing things that are not there (hallucinations)
  - feeling people are against you (paranoia)
  - feeling confused
  - other unusual changes in behavior or mood

955  
956 When you try to quit smoking, with or without bupropion, you may have symptoms that may be  
957 due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping,  
958 irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased  
959 heart rate, and increased appetite or weight gain. Some people have even experienced suicidal  
960 thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead  
961 to worsening of mental health problems that you already have, such as depression.

962

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

966

### 967 **What Other Important Information Should I Know About WELLBUTRIN?**

968

- 969 • **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN,**  
970 **especially in people:**

971

- with certain medical problems.

972

- who take certain medicines.

973

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

979

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

982

- 983 • **High blood pressure (hypertension). Some people get high blood pressure, that can be**  
984 **severe, while taking WELLBUTRIN.** The chance of high blood pressure may be higher if  
985 you also use nicotine replacement therapy (such as a nicotine patch) to help you stop  
986 smoking.
- 987 • **Severe allergic reactions. Some people have severe allergic reaction to WELLBUTRIN.**  
988 **Stop taking WELLBUTRIN and call your doctor right away** if you get a rash, itching,  
989 hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of  
990 the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious  
991 allergic reaction.
- 992 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
993 taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations  
994 (seeing or hearing things that are not there), paranoia (feeling that people are against you), or  
995 feeling confused. If this happens to you, call your doctor.

996

### 997 **What is WELLBUTRIN?**

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

1000

### 1001 **Who should not take WELLBUTRIN?**

1002 **Do not take WELLBUTRIN if you**

- 1003 • have or had a seizure disorder or epilepsy.
- 1004 • **are taking ZYBAN (used to help people stop smoking) or any other medicines that**
- 1005 **contain bupropion hydrochloride, such as WELLBUTRIN SR Sustained-Release**
- 1006 **Tablets or WELLBUTRIN XL Extended-Release Tablets.** Bupropion is the same active
- 1007 ingredient that is in WELLBUTRIN.
- 1008 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these
- 1009 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1010 • have taken within the last 14 days medicine for depression called a monoamine oxidase
- 1011 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine
- 1012 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 1013 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1014 • are allergic to the active ingredient in WELLBUTRIN, bupropion, or to any of the inactive
- 1015 ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN.
- 1016

### 1017 **What should I tell my doctor before using WELLBUTRIN?**

1018 Tell your doctor if you have ever had depression, suicidal thoughts or actions, or other mental  
1019 health problems. See “Antidepressant Medicines, Depression and Other Serious Mental Illnesses,  
1020 and Suicidal Thoughts or Actions.”

1021

- 1022 • **Tell your doctor about your other medical conditions including if you:**
- 1023 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN can harm
- 1024 your unborn baby.
- 1025 • **are breastfeeding.** WELLBUTRIN passes through your milk. It is not known if
- 1026 WELLBUTRIN can harm your baby.
- 1027 • **have liver problems,** especially cirrhosis of the liver.
- 1028 • have kidney problems.
- 1029 • have an eating disorder, such as anorexia nervosa or bulimia.
- 1030 • have had a head injury.
- 1031 • have had a seizure (convulsion, fit).
- 1032 • have a tumor in your nervous system (brain or spine).
- 1033 • have had a heart attack, heart problems, or high blood pressure.
- 1034 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1035 • drink a lot of alcohol.
- 1036 • abuse prescription medicines or street drugs.
- 1037 • **Tell your doctor about all the medicines you take,** including prescription and non-
- 1038 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
- 1039 chances of having seizures or other serious side effects if you take them while you are using
- 1040 WELLBUTRIN.
- 1041

1041

### 1042 **How should I take WELLBUTRIN?**

- 1043 • Take WELLBUTRIN exactly as prescribed by your doctor.
- 1044 • Take WELLBUTRIN at the same time each day.
- 1045 • Take your doses of WELLBUTRIN at least 6 hours apart.
- 1046 • You may take WELLBUTRIN with or without food.
- 1047 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
- 1048 take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN
- 1049 can increase your chance of having a seizure.
- 1050 • If you take too much WELLBUTRIN, or overdose, call your local emergency room or poison
- 1051 control center right away.
- 1052 • **Do not take any other medicines while using WELLBUTRIN unless your doctor has**
- 1053 **told you it is okay.**
- 1054 • It may take several weeks for you to feel that WELLBUTRIN is working. Once you feel
- 1055 better, it is important to keep taking WELLBUTRIN exactly as directed by your doctor. Call
- 1056 your doctor if you do not feel WELLBUTRIN is working for you.
- 1057 • Do not change your dose or stop taking WELLBUTRIN without talking with your doctor
- 1058 first.

1059

#### 1060 **What should I avoid while taking WELLBUTRIN?**

- 1061 • Do not drink a lot of alcohol while taking WELLBUTRIN. If you usually drink a lot of
- 1062 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking
- 1063 alcohol, you may increase your risk of having seizures.
- 1064 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN affects you.
- 1065 WELLBUTRIN can impair your ability to perform these tasks.

1066

#### 1067 **What are possible side effects of WELLBUTRIN?**

1068 WELLBUTRIN can cause serious side effects. Read this entire Medication Guide for more  
1069 information about these serious side effects.

1070

1071 The most common side effects of WELLBUTRIN are nervousness, constipation, trouble  
1072 sleeping, dry mouth, headache, nausea, vomiting, and shakiness (tremor).

1073

1074 If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your  
1075 medicine too close to bedtime.

1076

1077 These are not all the side effects of WELLBUTRIN. For a complete list, ask your doctor or  
1078 pharmacist.

1079

1080 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
1081 1-800-FDA-1088.

1082

1083 **How should I store WELLBUTRIN?**

- 1084 • Store WELLBUTRIN at room temperature. Store out of direct sunlight. Keep  
1085 WELLBUTRIN in its tightly closed bottle.

1086

1087 **General Information about WELLBUTRIN.**

- 1088 • Medicines are sometimes prescribed for purposes other than those listed in a Medication  
1089 Guide. Do not use WELLBUTRIN for a condition for which it was not prescribed. Do not  
1090 give WELLBUTRIN to other people, even if they have the same symptoms you have. It may  
1091 harm them. Keep WELLBUTRIN out of the reach of children.

1092

1093 This Medication Guide summarizes important information about WELLBUTRIN. For more  
1094 information, talk to your doctor. You can ask your doctor or pharmacist for information about  
1095 WELLBUTRIN that is written for health professionals.

1096

1097 **What are the ingredients in WELLBUTRIN?**

1098 Active ingredient: bupropion hydrochloride.

1099

1100 Inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake,  
1101 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and  
1102 titanium dioxide; 100-mg tablet – FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake,  
1103 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and  
1104 titanium dioxide.

1105

1106 WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, and PARNATE are registered  
1107 trademarks of GlaxoSmithKline.

1108 \*The following are registered trademarks of their respective manufacturers: NARDIL<sup>®</sup>/Warner  
1109 Lambert Company; MARPLAN<sup>®</sup>/Oxford Pharmaceutical Services, Inc; KALETRA<sup>®</sup>/Abbott  
1110 Laboratories.

1111

1112 **R<sub>x</sub> only**

1113

1114 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1115

1116 (Date of Issue)

1117 WLT: 6MG

1118

1119



1120

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PRESCRIBING INFORMATION

1  
2 **WELLBUTRIN SR<sup>®</sup>**  
3 **(bupropion hydrochloride)**  
4 **Sustained-Release Tablets**  
5

6 **WARNING**

7 **Suicidality and Antidepressant Drugs**

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

23 ***Use in Smoking Cessation Treatment:*** WELLBUTRIN<sup>®</sup>, WELLBUTRIN SR<sup>®</sup>, and  
24 WELLBUTRIN XL<sup>®</sup> are not approved for smoking cessation treatment, but bupropion under the  
25 name ZYBAN<sup>®</sup> is approved for this use. Serious neuropsychiatric events, including but not  
26 limited to depression, suicidal ideation, suicide attempt, and completed suicide have been  
27 reported in patients taking bupropion for smoking cessation. Some cases may have been  
28 complicated by the symptoms of nicotine withdrawal in patients who stopped smoking.  
29 Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including  
30 suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without  
31 medication. However, some of these symptoms have occurred in patients taking bupropion who  
32 continued to smoke.

33 All patients being treated with bupropion for smoking cessation treatment should be observed  
34 for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed  
35 mood, and suicide-related events, including ideation, behavior, and attempted suicide. These  
36 symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have  
37 been reported in some patients attempting to quit smoking while taking ZYBAN in the  
38 postmarketing experience. When symptoms were reported, most were during treatment with  
39 ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have  
40 occurred in patients with and without pre-existing psychiatric disease; some have experienced

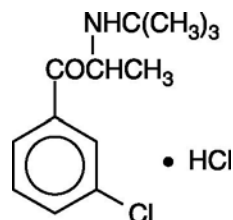
41 worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as  
42 schizophrenia, bipolar disorder, and major depressive disorder did not participate in the  
43 premarketing studies of ZYBAN.

44 **Advise patients and caregivers that the patient using bupropion for smoking cessation**  
45 **should stop taking bupropion and contact a healthcare provider immediately if agitation,**  
46 **hostility, depressed mood, or changes in thinking or behavior that are not typical for the**  
47 **patient are observed, or if the patient develops suicidal ideation or suicidal behavior.** In  
48 many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was  
49 reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and  
50 supportive care should be provided until symptoms resolve.

51 The risks of using bupropion for smoking cessation should be weighed against the benefits of  
52 its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking  
53 for as long as 6 months compared to treatment with placebo. The health benefits of quitting  
54 smoking are immediate and substantial. (See WARNINGS: Neuropsychiatric Symptoms and  
55 Suicide Risk in Smoking Cessation Treatment and PRECAUTIONS: Information for Patients.)

## 56 DESCRIPTION

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



65  
66  
67 WELLBUTRIN SR is supplied for oral administration as 100-mg (blue), 150-mg (purple),  
68 and 200-mg (light pink), film-coated, sustained-release tablets. Each tablet contains the labeled  
69 amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, cysteine  
70 hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene  
71 glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the  
72 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C Blue No. 2  
73 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40 Lake.

74 **CLINICAL PHARMACOLOGY**

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

80 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and  
81 pharmacokinetics of the individual enantiomers have not been studied. The mean elimination  
82 half-life ( $\pm$ SD) of bupropion after chronic dosing is 21 ( $\pm$ 9) hours, and steady-state plasma  
83 concentrations of bupropion are reached within 8 days. In a study comparing chronic dosing with  
84 WELLBUTRIN SR 150 mg twice daily to the immediate-release formulation of bupropion at  
85 100 mg 3 times daily, peak plasma concentrations of bupropion at steady state for  
86 WELLBUTRIN SR were approximately 85% of those achieved with the immediate-release  
87 formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak  
88 plasma concentration and AUCs for all 3 of the detectable bupropion metabolites. Thus, at steady  
89 state, WELLBUTRIN SR, given twice daily, and the immediate-release formulation of  
90 bupropion, given 3 times daily, are essentially bioequivalent for both bupropion and the 3  
91 quantitatively important metabolites.

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

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

100 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
101 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
102 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
103 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
104 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
105 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
106 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of  
107 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency  
108 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,  
109 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is  
110 one-half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-  
111 fold less potent than bupropion. This may be of clinical importance because the plasma  
112 concentrations of the metabolites are as high or higher than those of bupropion.

113 Because bupropion is extensively metabolized, there is the potential for drug-drug  
114 interactions, particularly with those agents that are metabolized by or which inhibit/induce the  
115 cytochrome P450IIB6 (CYP2B6) isoenzyme, such as ritonavir. In a healthy volunteer study,  
116 ritonavir at a dose of 100 mg twice daily reduced the AUC and  $C_{max}$  of bupropion by 22% and  
117 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the  
118 threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

119 In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the  
120 AUC and the  $C_{max}$  of bupropion by 66% and 62%, respectively. The exposure of the  
121 hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by  
122 50%, and the erythrohydrobupropion decreased by 68%.

123 In another healthy volunteer study, KALETRA<sup>®</sup>\* (lopinavir 400 mg/ritonavir 100 mg twice  
124 daily) decreased bupropion AUC and  $C_{max}$  by 57%. The AUC and  $C_{max}$  of hydroxybupropion  
125 were decreased by 50% and 31%, respectively (see PRECAUTIONS: Drug Interactions).

126 Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the  
127 potential for drug-drug interactions when bupropion is coadministered with drugs metabolized  
128 by this isoenzyme (see PRECAUTIONS: Drug Interactions).

129 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur  
130 approximately 6 hours after administration of WELLBUTRIN SR. Peak plasma concentrations  
131 of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state.  
132 The elimination half-life of hydroxybupropion is approximately 20 ( $\pm$ 5) hours, and its AUC at  
133 steady state is about 17 times that of bupropion. The times to peak concentrations for the  
134 erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the  
135 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 ( $\pm$ 10) and 37  
136 ( $\pm$ 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,  
137 respectively.

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

140 **Elimination:** Following oral administration of 200 mg of <sup>14</sup>C-bupropion in humans, 87% and  
141 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the  
142 fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent  
143 with the extensive metabolism of bupropion.

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

150 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was  
151 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in  
152 patients with mild-to-severe cirrhosis. The first study showed that the half-life of

153 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in  
154 8 healthy volunteers ( $32 \pm 14$  hours versus  $21 \pm 5$  hours, respectively). Although not statistically  
155 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be  
156 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for  
157 bupropion and the other metabolites in the 2 patient groups were minimal.

158 The second study showed no statistically significant differences in the pharmacokinetics of  
159 bupropion and its active metabolites in 9 patients with mild-to-moderate hepatic cirrhosis  
160 compared to 8 healthy volunteers. However, more variability was observed in some of the  
161 pharmacokinetic parameters for bupropion (AUC,  $C_{\max}$ , and  $T_{\max}$ ) and its active metabolites ( $t_{1/2}$ )  
162 in patients with mild-to-moderate hepatic cirrhosis. In addition, in patients with severe hepatic  
163 cirrhosis, the bupropion  $C_{\max}$  and AUC were substantially increased (mean difference: by  
164 approximately 70% and 3-fold, respectively) and more variable when compared to values in  
165 healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with  
166 severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion,  
167 the mean  $C_{\max}$  was approximately 69% lower. For the combined amino-alcohol isomers  
168 threohydrobupropion and erythrohydrobupropion, the mean  $C_{\max}$  was approximately 31% lower.  
169 The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for  
170 threo/erythrohydrobupropion. The median  $T_{\max}$  was observed 19 hours later for  
171 hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for  
172 hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively,  
173 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,  
174 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

175 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
176 renal impairment. An inter-study comparison between normal subjects and patients with end-  
177 stage renal failure demonstrated that the parent drug  $C_{\max}$  and AUC values were comparable in  
178 the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-  
179 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. A second  
180 study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR  
181  $30.9 \pm 10.8$  mL/min) showed that exposure to a single 150-mg dose of sustained-release  
182 bupropion was approximately 2-fold higher in patients with impaired renal function while levels  
183 of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar  
184 in the 2 groups. The elimination of bupropion and/or the major metabolites of bupropion may be  
185 reduced by impaired renal function (see PRECAUTIONS: Renal Impairment).

186 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in  
187 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on  
188 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed,  
189 compared to healthy volunteers.

190 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have not  
191 been fully characterized, but an exploration of steady-state bupropion concentrations from  
192 several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on

193 a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma  
194 concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the  
195 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger  
196 subjects. These data suggest there is no prominent effect of age on bupropion concentration;  
197 however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly  
198 are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS:  
199 Geriatric Use).

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

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

## 207 **CLINICAL TRIALS**

208 The efficacy of the immediate-release formulation of bupropion as a treatment for depression  
209 was established in two 4-week, placebo-controlled trials in adult inpatients with depression and  
210 in one 6-week, placebo-controlled trial in adult outpatients with depression. In the first study,  
211 patients were titrated in a bupropion dose range of 300 to 600 mg/day on a 3 times daily  
212 schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial  
213 demonstrated the effectiveness of the immediate-release formulation of bupropion on the  
214 Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from  
215 that scale, and the Clinical Global Impressions (CGI) severity score. A second study included  
216 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and  
217 placebo. This trial demonstrated the effectiveness of the immediate-release formulation of  
218 bupropion, but only at the 450-mg/day dose; the results were positive for the HDRS total score  
219 and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received  
220 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the  
221 effectiveness of the immediate-release formulation of bupropion on the HDRS total score, HDRS  
222 item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI  
223 improvement score.

224 Although there are not as yet independent trials demonstrating the antidepressant effectiveness  
225 of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence  
226 of the immediate-release and sustained-release forms of bupropion under steady-state conditions,  
227 i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 100 mg  
228 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and  
229 extent of absorption, for parent drug and metabolites.

230 In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder,  
231 recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg

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

## 239 **INDICATIONS AND USAGE**

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

241 The efficacy of bupropion in the treatment of a major depressive episode was established in  
242 two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of  
243 depressed outpatients whose diagnoses corresponded most closely to the Major Depression  
244 category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL  
245 PHARMACOLOGY).

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

253 The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to  
254 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial  
255 (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use  
256 WELLBUTRIN SR for extended periods should periodically reevaluate the long-term usefulness  
257 of the drug for the individual patient.

## 258 **CONTRAINDICATIONS**

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

260 WELLBUTRIN SR is contraindicated in patients treated with ZYBAN (bupropion  
261 hydrochloride) Sustained-Release Tablets; WELLBUTRIN (bupropion hydrochloride), the  
262 immediate-release formulation; WELLBUTRIN XL (bupropion hydrochloride), the extended-  
263 release formulation; or any other medications that contain bupropion because the incidence of  
264 seizure is dose dependent.

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

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

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

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

## 275 **WARNINGS**

276 **Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders:** Patients  
277 with major depressive disorder (MDD), both adult and pediatric, may experience worsening of  
278 their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual  
279 changes in behavior, whether or not they are taking antidepressant medications, and this risk may  
280 persist until significant remission occurs. Suicide is a known risk of depression and certain other  
281 psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.  
282 There has been a long-standing concern, however, that antidepressants may have a role in  
283 inducing worsening of depression and the emergence of suicidality in certain patients during the  
284 early phases of treatment. Pooled analyses of short-term placebo-controlled trials of  
285 antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal  
286 thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with  
287 major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not  
288 show an increase in the risk of suicidality with antidepressants compared to placebo in adults  
289 beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65  
290 and older.

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

302

303 **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

304

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

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

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

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

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

326 **Families and caregivers of patients being treated with antidepressants for major**  
327 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**  
328 **alerted about the need to monitor patients for the emergence of agitation, irritability,**  
329 **unusual changes in behavior, and the other symptoms described above, as well as the**  
330 **emergence of suicidality, and to report such symptoms immediately to healthcare**  
331 **providers. Such monitoring should include daily observation by families and caregivers.**

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

334 **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment:**  
335 WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL are not approved for smoking  
336 cessation treatment, but bupropion under the name ZYBAN is approved for this use. Serious  
337 neuropsychiatric symptoms have been reported in patients taking bupropion for smoking  
338 cessation (see **BOXED WARNING, ADVERSE REACTIONS**). **These have included**  
339 **changes in mood (including depression and mania), psychosis, hallucinations, paranoia,**  
340 **delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as**  
341 **suicidal ideation, suicide attempt, and completed suicide.** Some reported cases may have been  
342 complicated by the symptoms of nicotine withdrawal in patients who stopped smoking.  
343 Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including  
344 suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without  
345 medication. However, some of these symptoms have occurred in patients taking bupropion who  
346 continued to smoke. When symptoms were reported, most were during bupropion treatment, but  
347 some were following discontinuation of bupropion therapy.

348 These events have occurred in patients with and without pre-existing psychiatric disease;  
349 some have experienced worsening of their psychiatric illnesses. All patients being treated with  
350 bupropion as part of smoking cessation treatment should be observed for neuropsychiatric  
351 symptoms or worsening of pre-existing psychiatric illness.

352 Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major  
353 depressive disorder did not participate in the pre-marketing studies of ZYBAN.

354 **Advise patients and caregivers that the patient using bupropion for smoking cessation**  
355 **should stop taking bupropion and contact a healthcare provider immediately if agitation,**  
356 **depressed mood, or changes in behavior or thinking that are not typical for the patient are**  
357 **observed, or if the patient develops suicidal ideation or suicidal behavior. In many**  
358 **postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was**  
359 **reported, although in some cases the symptoms persisted, therefore, ongoing monitoring**  
360 **and supportive care should be provided until symptoms resolve.**

361 The risks of using bupropion for smoking cessation should be weighed against the benefits of  
362 its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking  
363 for as long as six months compared to treatment with placebo. The health benefits of quitting  
364 smoking are immediate and substantial.

365 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial  
366 presentation of bipolar disorder. It is generally believed (though not established in controlled  
367 trials) that treating such an episode with an antidepressant alone may increase the likelihood of  
368 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the  
369 symptoms described above represent such a conversion is unknown. However, prior to initiating  
370 treatment with an antidepressant, patients with depressive symptoms should be adequately  
371 screened to determine if they are at risk for bipolar disorder; such screening should include a  
372 detailed psychiatric history, including a family history of suicide, bipolar disorder, and

373 depression. It should be noted that WELLBUTRIN SR is not approved for use in treating bipolar  
374 depression.

375 **Bupropion-Containing Products:** Patients should be made aware that WELLBUTRIN SR  
376 contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation  
377 treatment, and that WELLBUTRIN SR should not be used in combination with ZYBAN, or any  
378 other medications that contain bupropion, such as WELLBUTRIN (bupropion hydrochloride),  
379 the immediate-release formulation or WELLBUTRIN XL (bupropion hydrochloride), the  
380 extended-release formulation.

381  
382 **Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures**  
383 **is also related to patient factors, clinical situations, and concomitant medications, which**  
384 **must be considered in selection of patients for therapy with WELLBUTRIN SR.**

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

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

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

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

403 **Data for WELLBUTRIN SR revealed a seizure incidence of approximately 0.1% (i.e.,**  
404 **3 of 3,100 patients followed prospectively) in patients treated at doses in a range of 100**  
405 **to 300 mg/day. It is not possible to know if the lower seizure incidence observed in this**  
406 **study involving the sustained-release formulation of bupropion resulted from the**  
407 **different formulation or the lower dose used. However, as noted above, the**  
408 **immediate-release and sustained-release formulations are bioequivalent with regard to**  
409 **both rate and extent of absorption during steady state (the most pertinent condition to**  
410 **estimating seizure incidence), since most observed seizures occur under steady-state**  
411 **conditions.**

- 412 • **Patient factors:** Predisposing factors that may increase the risk of seizure with  
413 bupropion use include history of head trauma or prior seizure, central nervous system  
414 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications  
415 that lower seizure threshold.
- 416 • **Clinical situations:** Circumstances associated with an increased seizure risk include,  
417 among others, excessive use of alcohol or sedatives (including benzodiazepines);  
418 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and  
419 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 420 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,  
421 theophylline, systemic steroids) are known to lower seizure threshold.

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

- 425 • the total daily dose of WELLBUTRIN SR does *not* exceed 400 mg,  
426 • the daily dose is administered twice daily, and  
427 • the rate of incrementation of dose is gradual.
- 428 • **No single dose should exceed 200 mg to avoid high peak concentrations of bupropion  
429 and/or its metabolites.**

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

434 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients  
435 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,  
436 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is  
437 likely to occur in such patients to a greater extent than usual. The dose should not exceed  
438 100 mg every day or 150 mg every other day in these patients (see CLINICAL  
439 PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

#### 444 **PRECAUTIONS**

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

447

448 **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%

449

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

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

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

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

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

465

466 **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%

467

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

473 **Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by symptoms such  
474 as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported  
475 in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing  
476 reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated

477 with bupropion. A patient should stop taking WELLBUTRIN SR and consult a doctor if  
478 experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives,  
479 chest pain, edema, and shortness of breath) during treatment.

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

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

487 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN<sup>®</sup>  
488 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-  
489 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher  
490 incidence of treatment-emergent hypertension in patients treated with the combination of  
491 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the  
492 combination of sustained-release bupropion and NTS had treatment-emergent hypertension  
493 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,  
494 and placebo, respectively. The majority of these patients had evidence of preexisting  
495 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and  
496 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension  
497 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure  
498 is recommended in patients who receive the combination of bupropion and nicotine replacement.

499 There is no clinical experience establishing the safety of WELLBUTRIN SR Tablets in  
500 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care  
501 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed  
502 patients who had previously developed orthostatic hypotension while receiving tricyclic  
503 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with  
504 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine  
505 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in  
506 2 patients for exacerbation of baseline hypertension.

507 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients  
508 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.  
509 WELLBUTRIN SR should be used with caution in patients with hepatic impairment (including  
510 mild-to-moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in  
511 patients with mild-to-moderate hepatic cirrhosis.

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

515 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
516 patients with renal impairment. An inter-study comparison between normal subjects and patients

517 with end-stage renal failure demonstrated that the parent drug  $C_{max}$  and AUC values were  
518 comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
519 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage  
520 renal failure. A second study, comparing normal subjects and patients with moderate-to-severe  
521 renal impairment (GFR  $30.9 \pm 10.8$  mL/min) showed that exposure to a single 150-mg dose of  
522 sustained-release bupropion was approximately 2-fold higher in patients with impaired renal  
523 function while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined)  
524 metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to  
525 active metabolites, which are further metabolized and subsequently excreted by the kidneys.  
526 WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced  
527 frequency and/or dose should be considered as bupropion and the metabolites of bupropion may  
528 accumulate in such patients to a greater extent than usual. The patient should be closely  
529 monitored for possible adverse effects that could indicate high drug or metabolite levels.

530 **Information for Patients:** Prescribers or other health professionals should inform patients,  
531 their families, and their caregivers about the benefits and risks associated with treatment with  
532 WELLBUTRIN SR and should counsel them in its appropriate use. A patient Medication Guide  
533 about “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal  
534 Thoughts or Actions,” “Quitting Smoking, Quit-Smoking Medication, Changes in Thinking and  
535 Behavior, Depression, and Suicidal Thoughts or Actions,” and “What Other Important  
536 Information Should I Know About WELLBUTRIN SR?” is available for WELLBUTRIN SR.  
537 The prescriber or health professional should instruct patients, their families, and their caregivers  
538 to read the Medication Guide and should assist them in understanding its contents. Patients  
539 should be given the opportunity to discuss the contents of the Medication Guide and to obtain  
540 answers to any questions they may have. The complete text of the Medication Guide is reprinted  
541 at the end of this document.

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

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

555 ***Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation***

556 ***Treatment:*** Although WELLBUTRIN SR is not indicated for smoking cessation treatment, it

557 contains the same active ingredient as ZYBAN which is approved for this use. Patients should be  
558 informed that quitting smoking, with or without ZYBAN, may be associated with nicotine  
559 withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing  
560 psychiatric illness. Furthermore, some patients have experienced changes in mood (including  
561 depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation,  
562 aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed  
563 suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation,  
564 hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if  
565 patients develop suicidal ideation or behavior, they should be urged to report these symptoms to  
566 their healthcare provider immediately.

567 **Bupropion-Containing Products:** Patients should be made aware that  
568 WELLBUTRIN SR contains the same active ingredient found in ZYBAN, used as an aid to  
569 smoking cessation treatment, and that WELLBUTRIN SR should not be used in combination  
570 with ZYBAN or any other medications that contain bupropion hydrochloride (such as  
571 WELLBUTRIN, the immediate-release formulation and WELLBUTRIN XL, the extended-  
572 release formulation).

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

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

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

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

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

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

591 Patients should be advised to swallow WELLBUTRIN SR tablets whole so that the release  
592 rate is not altered. Do not chew, divide, or crush tablets, as this may lead to an increased risk of  
593 adverse effects, including seizures.

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

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

598 Because bupropion is extensively metabolized, the coadministration of other drugs may affect  
599 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to  
600 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
601 interaction between WELLBUTRIN SR and drugs that are substrates of or inhibitors/inducers of  
602 the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and  
603 clopidogrel). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and  
604 fluvoxamine as well as nelfinavir and efavirenz inhibit the hydroxylation of bupropion. No  
605 clinical studies have been performed to evaluate this finding. The threohydrobupropion  
606 metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes.  
607 The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion  
608 and its active metabolites were studied in 24 healthy young male volunteers. Following oral  
609 administration of two 150-mg WELLBUTRIN SR tablets with and without 800 mg of  
610 cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected.  
611 However, there were 16% and 32% increases in the AUC and  $C_{max}$ , respectively, of the  
612 combined moieties of threohydrobupropion and erythrohydrobupropion.

613 In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice  
614 daily) or ritonavir 100 mg plus lopinavir 400 mg (KALETRA) twice daily reduced the exposure  
615 of bupropion and its major metabolites in a dose dependent manner by approximately 20% to  
616 80%. This effect is thought to be due to the induction of bupropion metabolism. Patients  
617 receiving ritonavir may need increased doses of bupropion, but the maximum recommended  
618 dose of bupropion should not be exceeded (see CLINICAL PHARMACOLOGY: Metabolism).

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

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

623 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
624 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to  
625 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.  
626 Nevertheless, there may be the potential for clinically important alterations of blood levels of  
627 coadministered drugs.

628 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most  
629 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are  
630 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this  
631 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a  
632 study of 15 male subjects (aged 19 to 35 years) who were extensive metabolizers of the CYP2D6  
633 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of  
634 50 mg desipramine increased the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of

635 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the  
636 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6  
637 has not been formally studied.

638 Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6  
639 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,  
640 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),  
641 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),  
642 should be approached with caution and should be initiated at the lower end of the dose range of  
643 the concomitant medication. If bupropion is added to the treatment regimen of a patient already  
644 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original  
645 medication should be considered, particularly for those concomitant medications with a narrow  
646 therapeutic index.

647 Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion  
648 increased the  $C_{max}$  and AUC of citalopram by 30% and 40%, respectively. Citalopram did not  
649 affect the pharmacokinetics of bupropion and its 3 metabolites.

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

652 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
653 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
654 Administration of WELLBUTRIN SR to patients receiving either levodopa or amantadine  
655 concurrently should be undertaken with caution, using small initial doses and gradual dose  
656 increases.

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

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

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

666 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies  
667 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These  
668 doses are approximately 7 and 2 times the maximum recommended human dose (MRHD),  
669 respectively, on a mg/m<sup>2</sup> basis. In the rat study there was an increase in nodular proliferative  
670 lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a  
671 mg/m<sup>2</sup> basis); lower doses were not tested. The question of whether or not such lesions may be  
672 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen  
673 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in  
674 either study.

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

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

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

687 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
688 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
689 there were no apparent adverse effects on offspring development.

690 One study has been conducted in pregnant women. This retrospective, managed-care database  
691 study assessed the risk of congenital malformations overall and cardiovascular malformations  
692 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
693 malformations following exposure to other antidepressants in the first trimester and bupropion  
694 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
695 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
696 showed no greater risk for congenital malformations overall or cardiovascular malformations  
697 specifically, following first trimester bupropion exposure compared to exposure to all other  
698 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of  
699 this study have not been corroborated. WELLBUTRIN SR should be used during pregnancy only  
700 if the potential benefit justifies the potential risk to the fetus.

701 **Labor and Delivery:** The effect of WELLBUTRIN SR on labor and delivery in humans is  
702 unknown.

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

707 **Pediatric Use:** Safety and effectiveness in the pediatric population have not been established  
708 (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk in Treating  
709 Psychiatric Disorders).

710 Anyone considering the use of WELLBUTRIN SR in a child or adolescent must balance the  
711 potential risks with the clinical need.

712 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with  
713 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were 65 and  
714 over and 47 were 75 and over. In addition, several hundred patients 65 and over participated in

715 clinical trials using the immediate-release formulation of bupropion (depression studies). No  
716 overall differences in safety or effectiveness were observed between these subjects and younger  
717 subjects, and other reported clinical experience has not identified differences in responses  
718 between the elderly and younger patients, but greater sensitivity of some older individuals cannot  
719 be ruled out.

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

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

## 729 **ADVERSE REACTIONS**

730 (See also WARNINGS and PRECAUTIONS.)

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

### 737 **Incidence in Controlled Trials With WELLBUTRIN SR: Adverse Events Associated** 738 **With Discontinuation of Treatment Among Patients Treated With**

739 **WELLBUTRIN SR:** In placebo-controlled clinical trials, 9% and 11% of patients treated with  
740 300 and 400 mg/day, respectively, of WELLBUTRIN SR and 4% of patients treated with  
741 placebo discontinued treatment due to adverse events. The specific adverse events in these trials  
742 that led to discontinuation in at least 1% of patients treated with either 300 or 400 mg/day of  
743 WELLBUTRIN SR and at a rate at least twice the placebo rate are listed in Table 4.  
744

745 **Table 4. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled 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%

746

747 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**  
 748 **Treated With WELLBUTRIN SR:** Table 5 enumerates treatment-emergent adverse events that  
 749 occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR and with  
 750 placebo in placebo-controlled trials. Events that occurred in either the 300- or 400-mg/day group  
 751 at an incidence of 1% or more and were more frequent than in the placebo group are included.  
 752 Reported adverse events were classified using a COSTART-based Dictionary.

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

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

764  
765

**Table 5. Treatment-Emergent Adverse Events in Placebo-Controlled Trials<sup>a</sup>**

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%
<b>Musculoskeletal</b>			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
<b>Nervous system</b>			
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%
<b>Respiratory</b>			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
<b>Skin</b>			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
<b>Special senses</b>			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
<b>Urogenital</b>			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage <sup>b</sup>	0%	2%	—
Urinary tract infection	1%	0%	—

766 <sup>a</sup> Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day  
767 of WELLBUTRIN SR, but equally or more frequently in the placebo group, were: abnormal  
768 dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea,  
769 dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and  
770 tooth disorder.

771 <sup>b</sup> Incidence based on the number of female patients.

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

773

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

775 Adverse events from Table 5 occurring in at least 5% of patients treated with  
776 WELLBUTRIN SR and at a rate at least twice the placebo rate are listed below for the 300- and  
777 400-mg/day dose groups.

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

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

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

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

789 Adverse events for which frequencies are provided below occurred in clinical trials with the  
790 sustained-release formulation of bupropion. The frequencies represent the proportion of patients  
791 who experienced a treatment-emergent adverse event on at least one occasion in  
792 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients  
793 who experienced an adverse event requiring discontinuation of treatment in an open-label  
794 surveillance study with WELLBUTRIN SR Tablets (n = 3,100). All treatment-emergent adverse  
795 events are included except those listed in Tables 2 through 5, those events listed in other  
796 safety-related sections, those adverse events subsumed under COSTART terms that are either  
797 overly general or excessively specific so as to be uninformative, those events not reasonably  
798 associated with the use of the drug, and those events that were not serious and occurred in fewer  
799 than 2 patients. Events of major clinical importance are described in the WARNINGS and  
800 PRECAUTIONS sections of the labeling.

801 Events are further categorized by body system and listed in order of decreasing frequency  
802 according to the following definitions of frequency: Frequent adverse events are defined as those  
803 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
804 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

827 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed  
828 was glycosuria.

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

831 **Nervous System:** Infrequent were abnormal coordination, decreased libido,  
832 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,  
833 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also  
834 observed were abnormal electroencephalogram (EEG), akinesia, aggression, aphasia, coma,  
835 completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria,  
836 extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction,  
837 neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive  
838 dyskinesia.

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

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

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

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

## 847 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

## 870 **OVERDOSAGE**

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

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

881 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
882 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first

883 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
884 Induction of emesis is not recommended.

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

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

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

## 896 **DOSAGE AND ADMINISTRATION**

897 **General Dosing Considerations:** It is particularly important to administer  
898 WELLBUTRIN SR in a manner most likely to minimize the risk of seizure (see WARNINGS).  
899 Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia,  
900 often seen during the initial days of treatment, are to be minimized. If necessary, these effects  
901 may be managed by temporary reduction of dose or the short-term administration of an  
902 intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond  
903 the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If  
904 distressing, untoward effects supervene, dose escalation should be stopped. WELLBUTRIN SR  
905 should be swallowed whole and not crushed, divided, or chewed, as this may lead to an increased  
906 risk of adverse effects including seizures.

907 **Initial Treatment:** The usual adult target dose for WELLBUTRIN SR is 300 mg/day, given as  
908 150 mg twice daily. Dosing with WELLBUTRIN SR should begin at 150 mg/day given as a  
909 single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to  
910 the 300-mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of  
911 dosing. There should be an interval of at least 8 hours between successive doses.

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

917 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require  
918 several months or longer of sustained pharmacological therapy beyond response to the acute  
919 episode. In a study in which patients with major depressive disorder, recurrent type, who had  
920 responded during 8 weeks of acute treatment with WELLBUTRIN SR were assigned randomly  
921 to placebo or to the same dose of WELLBUTRIN SR (150 mg twice daily) during 44 weeks of

922 maintenance treatment as they had received during the acute stabilization phase, longer-term  
923 efficacy was demonstrated (see CLINICAL TRIALS under CLINICAL PHARMACOLOGY).  
924 Based on these limited data, it is unknown whether or not the dose of WELLBUTRIN SR needed  
925 for maintenance treatment is identical to the dose needed to achieve an initial response. Patients  
926 should be periodically reassessed to determine the need for maintenance treatment and the  
927 appropriate dose for such treatment.

928 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN SR  
929 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should  
930 not exceed 100 mg every day or 150 mg every other day in these patients. WELLBUTRIN SR  
931 should be used with caution in patients with hepatic impairment (including mild-to-moderate  
932 hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with  
933 mild-to-moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY, WARNINGS, and  
934 PRECAUTIONS).

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

## 938 **HOW SUPPLIED**

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

942 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are  
943 purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of  
944 60 (NDC 0173-0135-55) tablets.

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

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

950

951

## **MEDICATION GUIDE**

952

### **WELLBUTRIN SR<sup>®</sup> (WELL byu-trin)**

953

### **(bupropion hydrochloride) Sustained-Release Tablets**

954

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

959

960 **IMPORTANT: Be sure to read the three sections of this Medication Guide. The first**  
961 **section is about the risk of suicidal thoughts and actions with antidepressant medicines; the**  
962 **second section is about the risk of changes in thinking and behavior, depression and**  
963 **suicidal thoughts or actions with medicines used to quit smoking; and the third section is**  
964 **entitled “What Other Important Information Should I Know About WELLBUTRIN SR?”**  
965

966 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and**  
967 **Suicidal Thoughts or Actions**  
968

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

- 972 • all risks and benefits of treatment with antidepressant medicines
  - 973 • all treatment choices for depression or other serious mental illness
- 974

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

- 977 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**  
978 **teenagers, and young adults within the first few months of treatment.**
  - 979 **2. Depression and other serious mental illnesses are the most important causes of suicidal**  
980 **thoughts and actions. Some people may have a particularly high risk of having suicidal**  
981 **thoughts or actions.** These include people who have (or have a family history of) bipolar  
982 illness (also called manic-depressive illness) or suicidal thoughts or actions.
  - 983 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**  
984 **family member?**
    - 985 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,  
986 thoughts, or feelings. This is very important when an antidepressant medicine is started or  
987 when the dose is changed.
    - 988 • Call the healthcare provider right away to report new or sudden changes in mood,  
989 behavior, thoughts, or feelings.
    - 990 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare  
991 provider between visits as needed, especially if you have concerns about symptoms.
- 992

993 **Call a healthcare provider right away if you or your family member has any of the**  
994 **following symptoms, especially if they are new, worse, or worry you:**  
995

- 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

996

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

998 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**

999 Stopping an antidepressant medicine suddenly can cause other symptoms.

1000 • **Antidepressants are medicines used to treat depression and other illnesses.** It is

1001 important to discuss all the risks of treating depression and also the risks of not treating it.

1002 Patients and their families or other caregivers should discuss all treatment choices with the  
1003 healthcare provider, not just the use of antidepressants.

1004 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the  
1005 side effects of the medicine prescribed for you or your family member.

1006 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines  
1007 that you or your family member takes. Keep a list of all medicines to show the healthcare  
1008 provider. Do not start new medicines without first checking with your healthcare provider.

1009 • **Not all antidepressant medicines prescribed for children are FDA approved for use in  
1010 children.** Talk to your child's healthcare provider for more information.

1011

1012 WELLBUTRIN SR has not been studied in children under the age of 18 and is not approved for  
1013 use in children and teenagers.

1014

1015 **Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior,  
1016 Depression, and Suicidal Thoughts or Actions**

1017

1018 This section of the Medication Guide is only about the risk of changes in thinking and behavior,  
1019 depression and suicidal thoughts or actions with drugs used to quit smoking.

1020

1021 Although WELLBUTRIN SR is not a treatment for quitting smoking, it contains the same active  
1022 ingredient (bupropion hydrochloride) as ZYBAN<sup>®</sup> which is used to help patients quit smoking.

1023

1024 Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or  
1025 actions while taking bupropion to help them quit smoking. These symptoms can develop during  
1026 treatment with bupropion or after stopping treatment with bupropion.

1027

1028 If you, your family member, or your caregiver notice agitation, hostility, depression, or changes  
1029 in thinking or behavior that are not typical for you, or you have any of the following symptoms,  
1030 stop taking bupropion and call your healthcare provider right away:

1031

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

1032

1033 When you try to quit smoking, with or without bupropion, you may have symptoms that may be  
1034 due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping,  
1035 irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased  
1036 heart rate, and increased appetite or weight gain. Some people have even experienced suicidal  
1037 thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead  
1038 to worsening of mental health problems that you already have, such as depression.

1039

1040 Before taking bupropion, tell your healthcare provider if you have ever had depression or other  
1041 mental illnesses. You should also tell your doctor about any symptoms you had during other  
1042 times you tried to quit smoking, with or without bupropion.

1043

#### 1044 **What Other Important Information Should I Know About WELLBUTRIN SR?**

1045

1046 • **Seizures: There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN SR,**  
1047 **especially in people:**

1048

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

1049

1050

1051 The chance of having seizures increases with higher doses of WELLBUTRIN SR. For more  
1052 information, see the sections “Who should not take WELLBUTRIN SR?” and “What should  
1053 I tell my doctor before using WELLBUTRIN SR?” Tell your doctor about all of your  
1054 medical conditions and all the medicines you take. **Do not take any other medicines while  
1055 you are using WELLBUTRIN SR unless your doctor has said it is okay to take them.**

1056

1057 **If you have a seizure while taking WELLBUTRIN SR, stop taking the tablets and call**  
1058 **your doctor right away.** Do not take WELLBUTRIN SR again if you have a seizure.

1059

- 1060 • **High blood pressure (hypertension).** Some people get high blood pressure, that can be  
1061 **severe, while taking WELLBUTRIN SR.** The chance of high blood pressure may be higher  
1062 if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop  
1063 smoking.
- 1064 • **Severe allergic reactions. Some people have severe allergic reaction to**  
1065 **WELLBUTRIN SR. Stop taking WELLBUTRIN SR and call your doctor right away** if  
1066 you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or  
1067 around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These  
1068 could be signs of a serious allergic reaction.
- 1069 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1070 taking WELLBUTRIN SR, including delusions (believe you are someone else),  
1071 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are  
1072 against you), or feeling confused. If this happens to you, call your doctor.
- 1073

#### 1074 **What is WELLBUTRIN SR?**

1075 WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type of  
1076 depression called major depressive disorder.

1077

#### 1078 **Who should not take WELLBUTRIN SR?**

##### 1079 **Do not take WELLBUTRIN SR if you**

- 1080 • have or had a seizure disorder or epilepsy.
- 1081 • **are taking ZYBAN<sup>®</sup> (used to help people stop smoking) or any other medicines that**  
1082 **contain bupropion hydrochloride, such as WELLBUTRIN<sup>®</sup> Tablets or WELLBUTRIN**  
1083 **XL<sup>®</sup> Extended-Release Tablets.** Bupropion is the same active ingredient that is in  
1084 WELLBUTRIN SR.
- 1085 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
1086 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1087 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
1088 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
1089 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 1090 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1091 • are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the  
1092 inactive ingredients. See the end of this leaflet for a complete list of ingredients in  
1093 WELLBUTRIN SR.
- 1094

#### 1095 **What should I tell my doctor before using WELLBUTRIN SR?**

1096 Tell your doctor if you have ever had depression, suicidal thoughts or actions, or other mental  
1097 health problems. See “Antidepressant Medicines, Depression and Other Serious Mental Illnesses,  
1098 and Suicidal Thoughts or Actions.”

- 1099 • **Tell your doctor about your other medical conditions including if you:**

- 1100 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN SR can
- 1101 harm your unborn baby.
- 1102 • **are breastfeeding.** WELLBUTRIN SR passes through your milk. It is not known if
- 1103 WELLBUTRIN SR can harm your baby.
- 1104 • **have liver problems,** especially cirrhosis of the liver.
- 1105 • have kidney problems.
- 1106 • have an eating disorder such as anorexia nervosa or bulimia.
- 1107 • have had a head injury.
- 1108 • have had a seizure (convulsion, fit).
- 1109 • have a tumor in your nervous system (brain or spine).
- 1110 • have had a heart attack, heart problems, or high blood pressure.
- 1111 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1112 • drink a lot of alcohol.
- 1113 • abuse prescription medicines or street drugs.
- 1114 • **Tell your doctor about all the medicines you take,** including prescription and non-
- 1115 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
- 1116 chances of having seizures or other serious side effects if you take them while you are using
- 1117 WELLBUTRIN SR.

1118

#### 1119 **How should I take WELLBUTRIN SR?**

- 1120 • Take WELLBUTRIN SR exactly as prescribed by your doctor.
- 1121 • **Do not chew, cut, or crush WELLBUTRIN SR tablets.** If you do, the medicine will be
- 1122 released into your body too quickly. If this happens you may be more likely to get side
- 1123 effects including seizures. You must swallow the tablets whole. **Tell your doctor if you**
- 1124 **cannot swallow medicine tablets.**
- 1125 • Take WELLBUTRIN SR at the same time each day.
- 1126 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 1127 • You may take WELLBUTRIN SR with or without food.
- 1128 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
- 1129 take your next tablet at the regular time. **This is very important.** Too much
- 1130 WELLBUTRIN SR can increase your chance of having a seizure.
- 1131 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or
- 1132 poison control center right away.
- 1133 • **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has**
- 1134 **told you it is okay.**
- 1135 • It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel
- 1136 better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor.
- 1137 Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- 1138 • Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor
- 1139 first.

1140

1141 **What should I avoid while taking WELLBUTRIN SR?**

- 1142 • Do not drink a lot of alcohol while taking WELLBUTRIN SR. If you usually drink a lot of  
1143 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking  
1144 alcohol, you may increase your chance of having seizures.  
1145 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects  
1146 you. WELLBUTRIN SR can impair your ability to perform these tasks.

1147

1148 **What are possible side effects of WELLBUTRIN SR?**

1149 WELLBUTRIN SR can cause serious side effects. Read this entire Medication Guide for more  
1150 information about these serious side effects.

1151

1152 The most common side effects of WELLBUTRIN SR are loss of appetite, dry mouth, skin rash,  
1153 sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble  
1154 sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

1155

1156 If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your  
1157 medicine too close to bedtime.

1158

1159 These are not all the side effects of WELLBUTRIN SR. For a complete list, ask your doctor or  
1160 pharmacist.

1161

1162 Call your doctor for medical advice about side effects. You may report side effects to FDA at  
1163 1-800-FDA-1088.

1164

1165 **How should I store WELLBUTRIN SR?**

- 1166 • Store WELLBUTRIN SR at room temperature. Store out of direct sunlight. Keep  
1167 WELLBUTRIN SR in its tightly closed bottle.  
1168 • WELLBUTRIN SR tablets may have an odor.

1169

1170 **General Information about WELLBUTRIN SR.**

1171 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.  
1172 Do not use WELLBUTRIN SR for a condition for which it was not prescribed. Do not give  
1173 WELLBUTRIN SR to other people, even if they have the same symptoms you have. It may harm  
1174 them. Keep WELLBUTRIN SR out of the reach of children.

1175

1176 This Medication Guide summarizes important information about WELLBUTRIN SR. For more  
1177 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
1178 WELLBUTRIN SR that is written for health professionals.

1179

1180 **What are the ingredients in WELLBUTRIN SR?**

1181 Active ingredient: bupropion hydrochloride.

1182

1183 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1184 microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In  
1185 addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C  
1186 Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40  
1187 Lake. The tablets are printed with edible black ink.

1188

1189 WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, ZYBAN, and PARNATE are  
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1193 Laboratories.

1194

1195 **R<sub>x</sub>only**

1196

1197 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1198

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