

WELLBUTRIN[®]
(bupropion hydrochloride)
Tablets

WARNING

Suicidality and Antidepressant Drugs

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

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

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

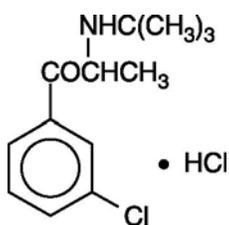
41 worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as
42 schizophrenia, bipolar disorder, and major depressive disorder did not participate in the
43 premarketing studies of ZYBAN.

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 C₁₃H₁₈ClNO•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:



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

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[®]* (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 ¹⁴C-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 ± 14 hours versus 21 ± 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 ± 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[®] (bupropion
234 hydrochloride) Sustained-Release Tablets; WELLBUTRIN SR[®] (bupropion hydrochloride), the
235 sustained-release formulation; WELLBUTRIN XL[®] (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 ± 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/m² 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/m²
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/m² 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^a (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 ^a 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® (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[®] 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

988 • **Severe allergic reactions. Some people have severe allergic reaction to WELLBUTRIN.**
989 **Stop taking WELLBUTRIN and call your doctor right away** if you get a rash, itching,
990 hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of
991 the lips or tongue, chest pain, or have trouble breathing. These could be signs of a serious
allergic reaction.

992

993 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while
994 taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations
995 (seeing or hearing things that are not there), paranoia (feeling that people are against you), or
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^{®*} (phenelzine sulfate), PARNATE[®] (tranylcypromine
- 1012 sulfate), or MARPLAN^{®*} (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

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[®]/Warner
1109 Lambert Company; MARPLAN[®]/Oxford Pharmaceutical Services, Inc; KALETRA[®]/Abbott
1110 Laboratories.

1111

1112 **R_x 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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1132
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1
2 **WELLBUTRIN SR[®]**
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[®], WELLBUTRIN SR[®], and
24 WELLBUTRIN XL[®] are not approved for smoking cessation treatment, but bupropion under the
25 name ZYBAN[®] 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

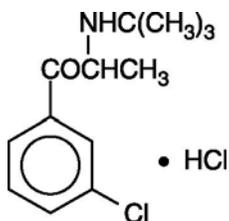
41 worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as
42 schizophrenia, bipolar disorder, and major depressive disorder did not participate in the
43 premarketing studies of ZYBAN.

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 C₁₃H₁₈ClNO•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:



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[®]* (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 ¹⁴C-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 ± 14 hours versus 21 ± 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 ± 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[®]
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 ± 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^2 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^2 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/m² 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/m²
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/m² 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	WELLBUTRIN SR	Placebo (n = 385)
	300 mg/day (n = 376)	400 mg/day (n = 114)	
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

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^a**

Body System/ Adverse Event	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%

Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage ^b	0%	2%	—
Urinary tract infection	1%	0%	—

766 ^a 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 ^b 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® (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[®] 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[®] (used to help people stop smoking) or any other medicines that**
1082 **contain bupropion hydrochloride, such as WELLBUTRIN[®] Tablets or WELLBUTRIN**
1083 **XL[®] 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^{®*} (phenelzine sulfate), PARNATE[®] (tranylcypromine
1089 sulfate), or MARPLAN^{®*} (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.

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What should I avoid while taking WELLBUTRIN SR?

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

What are possible side effects of WELLBUTRIN SR?

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

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

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

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

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

How should I store WELLBUTRIN SR?

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

General Information about WELLBUTRIN SR.

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

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

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
1190 registered trademarks of GlaxoSmithKline.

1191 *The following are registered trademarks of their respective manufacturers: NARDIL[®]/Warner
1192 Lambert Company; MARPLAN[®]/Oxford Pharmaceutical Services, Inc.; KALETRA[®]/Abbott
1193 Laboratories.

1194

1195 **R_xonly**

1196

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

1198

1199 (Date of Issue)

1200 WLS: 6MG

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1202

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