

PRESCRIBING INFORMATION

WELLBUTRIN[®]
(bupropion hydrochloride)
Tablets

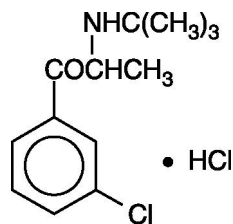
Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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 and PRECAUTIONS: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

WELLBUTRIN (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The empirical formula is C₁₃H₁₈ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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

42 CLINICAL PHARMACOLOGY

43 **Pharmacodynamics:** The neurochemical mechanism of the antidepressant effect of
44 bupropion is not known. Bupropion is a relatively weak inhibitor of the neuronal uptake of
45 norepinephrine, ~~serotonin~~, and dopamine, and does not inhibit monoamine oxidase or the
46 re-uptake of serotonin.

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

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

53 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacological activity and
54 pharmacokinetics of the individual enantiomers have not been studied. In humans, following oral
55 administration of WELLBUTRIN, peak plasma bupropion concentrations are usually achieved
56 within 2 hours, followed by a biphasic decline. The terminal phase has a mean half-life of
57 14 hours, with a range of 8 to 24 hours. The distribution phase has a mean half-life of 3 to
58 4 hours. The mean elimination half-life (\pm SD) of bupropion after chronic dosing is 21 (\pm 9)
59 hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma
60 bupropion concentrations are dose-proportional following single doses of 100 to 250 mg;
61 however, it is not known if the proportionality between dose and plasma level is maintained in
62 chronic use.

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

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

71 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been
72 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group
73 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,

74 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome
75 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,
76 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.
77 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-
78 chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and
79 toxicity of the metabolites relative to bupropion have not been fully characterized. However, it
80 has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one
81 half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold
82 less potent than bupropion. This may be of clinical importance because their plasma
83 concentrations are as high or higher than those of bupropion.

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

89 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur
90 approximately 3 hours after administration of WELLBUTRIN Tablets. Peak plasma
91 concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug
92 at steady state. The elimination half-life of hydroxybupropion is approximately 20 (\pm 5) hours,
93 and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations
94 for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the
95 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (\pm 10) and
96 37 (\pm 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,
97 respectively.

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

100 **Elimination:** Following oral administration of 200 mg of ¹⁴C-bupropion in humans, 87% and
101 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the
102 fraction of the oral dose of WELLBUTRIN excreted unchanged was only 0.5%, a finding
103 consistent with the extensive metabolism of bupropion.

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

110 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was
111 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in
112 patients with mild to severe cirrhosis. The first study showed that the half-life of
113 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in

114 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically
115 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
116 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life
117 for bupropion and the other metabolites in the 2 patient groups were minimal.

118 The second study showed that there were no statistically significant differences in the
119 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate
120 hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in
121 some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active
122 metabolites (t_{1/2}) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with
123 severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean
124 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to
125 values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients
126 with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite
127 hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-
128 alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was
129 approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion
130 and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours
131 later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean
132 half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold,
133 respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers (see
134 WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

135 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with
136 renal impairment. An inter-study comparison between normal subjects and patients with end-
137 stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in
138 the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3-
139 and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. The
140 elimination of the major metabolites of bupropion may be reduced by impaired renal function
141 (see PRECAUTIONS: Renal Impairment).

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

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

154 are at increased risk for accumulation of bupropion and its metabolites (see PRECAUTIONS:
155 Geriatric Use).

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

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

163 **INDICATIONS AND USAGE**

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

170 The efficacy of WELLBUTRIN has been established in 3 placebo-controlled trials, including
171 2 of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks'
172 duration in depressed outpatients. The depressive disorder of the patients studied corresponds
173 most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

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

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

184 **CONTRAINDICATIONS**

185 WELLBUTRIN is contraindicated in patients with a seizure disorder.

186 WELLBUTRIN is contraindicated in patients treated with ZYBAN[®] (bupropion
187 hydrochloride) Sustained-Release Tablets; WELLBUTRIN SR[®] (bupropion hydrochloride), the
188 sustained-release formulation; WELLBUTRIN XL[®] (bupropion hydrochloride), the extended-
189 release formulation; or any other medications that contain bupropion because the incidence of
190 seizure is dose dependent.

191 WELLBUTRIN is contraindicated in patients with a current or prior diagnosis of bulimia or
192 anorexia nervosa because of a higher incidence of seizures noted in such patients treated with
193 WELLBUTRIN.

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

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

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

201 **WARNINGS**

202 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
203 both adult and pediatric, may experience worsening of their depression and/or the emergence of
204 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
205 are taking antidepressant medications, and this risk may persist until significant remission
206 occurs. There has been a long-standing concern that antidepressants may have a role in inducing
207 worsening of depression and the emergence of suicidality in certain patients. Antidepressants
208 increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children
209 and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

210 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and
211 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of
212 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events
213 representing suicidal behavior or thinking (suicidality) during the first few months of treatment
214 in those receiving antidepressants. The average risk of such events in patients receiving
215 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk
216 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of
217 suicidality was most consistently observed in the MDD trials, but there were signals of risk
218 arising from some trials in other psychiatric indications (obsessive compulsive disorder and
219 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown
220 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several
221 months. It is also unknown whether the suicidality risk extends to adults.

222 **All pediatric patients being treated with antidepressants for any indication should be**
223 **observed closely for clinical worsening, suicidality, and unusual changes in behavior,**
224 **especially during the initial few months of a course of drug therapy, or at times of dose**
225 **changes, either increases or decreases. Such observation would generally include at least**
226 **weekly face-to-face contact with patients or their family members or caregivers during the**
227 **first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at**
228 **12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may**
229 **be appropriate between face-to-face visits.**

230 **Adults with MDD or co-morbid depression in the setting of other psychiatric illness**
231 **being treated with antidepressants should be observed similarly for clinical worsening and**
232 **suicidality, especially during the initial few months of a course of drug therapy, or at times**
233 **of dose changes, either increases or decreases.**

234 **In addition, patients with a history of suicidal behavior or thoughts, those patients**
235 **exhibiting a significant degree of suicidal ideation prior to commencement of treatment,**
236 **and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and**
237 **should receive careful monitoring during treatment.**

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

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

250 **Families and caregivers of pediatric patients being treated with antidepressants for**
251 **major depressive disorder or other indications, both psychiatric and nonpsychiatric,**
252 **should be alerted about the need to monitor patients for the emergence of agitation,**
253 **irritability, unusual changes in behavior, and the other symptoms described above, as well**
254 **as the emergence of suicidality, and to report such symptoms immediately to health care**
255 **providers. Such monitoring should include daily observation by families and caregivers.**
256 Prescriptions for WELLBUTRIN should be written for the smallest quantity of tablets consistent
257 with good patient management, in order to reduce the risk of overdose. Families and caregivers
258 of adults being treated for depression should be similarly advised.

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

269 Patients should be made aware that WELLBUTRIN contains the same active ingredient
270 found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN
271 should not be used in combination with ZYBAN, or any other medications that contain
272 bupropion, such as WELLBUTRIN SR (bupropion hydrochloride), the sustained-release
273 formulation or WELLBUTRIN XL (bupropion hydrochloride), the extended-release
274 formulation.

275

276 **Seizures:** Bupropion is associated with seizures in approximately 0.4% (4/1,000) of
277 patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of
278 other marketed antidepressants by as much as 4-fold. This relative risk is only an
279 approximate estimate because no direct comparative studies have been conducted. The
280 estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and
281 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third
282 the maximum recommended daily dose (450 mg). Given the wide variability among
283 individuals and their capacity to metabolize and eliminate drugs this disproportionate
284 increase in seizure incidence with dose incrementation calls for caution in dosing.

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

290 A separate, prospective study was conducted to determine the incidence of seizure
291 during an 8-week treatment exposure in approximately 3,200 additional patients who
292 received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond
293 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment
294 period and 5 seizures were reported in patients continuing treatment beyond 8 weeks,
295 resulting in a total seizure incidence of 0.4%.

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

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

- 304 • **Patient factors:** Predisposing factors that may increase the risk of seizure with
305 bupropion use include history of head trauma or prior seizure, central nervous system
306 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications
307 that lower seizure threshold.

308 • **Clinical situations:** Circumstances associated with an increased seizure risk include,
309 among others, excessive use of alcohol or sedatives (including benzodiazepines);
310 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and
311 anorectics; and diabetes treated with oral hypoglycemics or insulin.

312 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,
313 theophylline, systemic steroids) are known to lower seizure threshold.

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

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

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

325 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients
326 with severe hepatic cirrhosis. In these patients a reduced dose and/or frequency is required,
327 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is
328 likely to occur in such patients to a greater extent than usual. The dose should not exceed
329 75 mg once a day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS,
330 and DOSAGE AND ADMINISTRATION).

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

335 PRECAUTIONS

336 **General: Agitation and Insomnia:** A substantial proportion of patients treated with
337 WELLBUTRIN experience some degree of increased restlessness, agitation, anxiety, and
338 insomnia, especially shortly after initiation of treatment. In clinical studies, these symptoms were
339 sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. In
340 approximately 2% of patients, symptoms were sufficiently severe to require discontinuation of
341 treatment with WELLBUTRIN.

342 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Depressed
343 patients treated with WELLBUTRIN have been reported to show a variety of neuropsychiatric
344 signs and symptoms including delusions, hallucinations, psychosis, concentration disturbance,
345 paranoia, and confusion. Because of the uncontrolled nature of many studies, it is impossible to
346 provide a precise estimate of the extent of risk imposed by treatment with WELLBUTRIN. In

347 several cases, neuropsychiatric phenomena abated upon dose reduction and/or withdrawal of
348 treatment.

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

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

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

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

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

373 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN[®]
374 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-
375 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher
376 incidence of treatment-emergent hypertension in patients treated with the combination of
377 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the
378 combination of sustained-release bupropion and NTS had treatment-emergent hypertension
379 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,
380 and placebo, respectively. The majority of these patients had evidence of preexisting
381 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1
382 patient (0.4%) treated with NTS had study medication discontinued due to hypertension
383 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure
384 is recommended in patients who receive the combination of bupropion and nicotine replacement.

385 There is no clinical experience establishing the safety of WELLBUTRIN in patients with a
386 recent history of myocardial infarction or unstable heart disease. Therefore, care should be

387 exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who
388 had previously developed orthostatic hypotension while receiving tricyclic antidepressants and
389 was also generally well tolerated in a group of 36 depressed inpatients with stable congestive
390 heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in
391 the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for
392 exacerbation of baseline hypertension.

393 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients with
394 severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required.
395 WELLBUTRIN should be used with caution in patients with hepatic impairment (including mild
396 to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in
397 patients with mild to moderate hepatic cirrhosis.

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

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

412 **Information for Patients:** Prescribers or other health professionals should inform patients,
413 their families, and their caregivers about the benefits and risks associated with treatment with
414 WELLBUTRIN and should counsel them in its appropriate use. A patient-Medication Guide
415 about using antidepressants in children and teenagers and important information about using
416 WELLBUTRIN will be dispensed by the pharmacist with each new prescription and refill of
417 About Using Antidepressants in Children and Teenagers is available for WELLBUTRIN. The
418 prescriber or health professional should instruct patients, their families, and their caregivers to
419 read the Medication Guide and should assist them in understanding its contents. Patients should
420 be given the opportunity to discuss the contents of the Medication Guide and to obtain answers
421 to any questions they may have. The complete text of the Medication Guide is reprinted at the
422 end of this document. ~~Additional important information concerning WELLBUTRIN is provided~~
423 ~~in a tear-off leaflet entitled "Patient Information" at the end of this labeling.~~

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

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

437 Patients should be made aware that WELLBUTRIN contains the same active ingredient found
438 in ZYBAN, used as an aid to smoking cessation, and that WELLBUTRIN should not be used in
439 combination with ZYBAN or any other medications that contain bupropion hydrochloride (such
440 as WELLBUTRIN SR, the sustained-release formulation and WELLBUTRIN XL, the extended-
441 release formulation).

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

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

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

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

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

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

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

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

463 Because bupropion is extensively metabolized, the coadministration of other drugs may affect
464 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to
465 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug
466 interaction between WELLBUTRIN and drugs that are the substrates or inhibitors of the

467 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro
468 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,
469 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been
470 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not
471 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant
472 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites
473 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg
474 sustained-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of
475 bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases
476 in the AUC and C_{max} , respectively, of the combined moieties of threohydrobupropion and
477 erythrohydrobupropion.

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

480 Multiple oral doses of bupropion had no statistically significant effects on the single dose
481 pharmacokinetics of lamotrigine in 12 healthy volunteers, ~~and was associated with a slight~~
482 ~~increase in the AUC (15%) of lamotrigine glucuronide.~~

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

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

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

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

509 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse
510 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.

511 Administration of WELLBUTRIN Tablets to patients receiving either levodopa or amantadine
512 concurrently should be undertaken with caution, using small initial doses and small gradual dose
513 increases.

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

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

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

523 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies
524 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat
525 study there was an increase in nodular proliferative lesions of the liver at doses of 100 to
526 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be
527 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen
528 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in
529 either study.

530 Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in
531 some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not
532 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance
533 of these results in estimating the risk of human exposure to therapeutic doses is unknown.

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

536 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. In studies conducted in rats and
537 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively
538 (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively,
539 on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity
540 was found in either species; however, in rabbits, slightly increased incidences of fetal
541 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,
542 approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal weights were
543 seen at 50 mg/kg and greater.

544 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately
545 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy and lactation,
546 there were no apparent adverse effects on offspring development.

547 One study has been conducted in pregnant women. This retrospective, managed-care database
548 study assessed the risk of congenital malformations overall, and cardiovascular malformations
549 specifically, following exposure to bupropion in the first trimester compared to the risk of these
550 malformations following exposure to other antidepressants in the first trimester and bupropion

551 outside of the first trimester. This study included 7,005 infants with antidepressant exposure
552 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study
553 showed no greater risk for congenital malformations overall, or cardiovascular malformations
554 specifically, following first trimester bupropion exposure compared to exposure to all other
555 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of
556 this study have not been corroborated. WELLBUTRIN should be used during pregnancy only if
557 the potential benefit justifies the potential risk to the fetus.

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

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

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

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

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

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

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

588

589 **ADVERSE REACTIONS** (see also WARNINGS and PRECAUTIONS)

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

592 Adverse events were sufficiently troublesome to cause discontinuation of treatment with
593 WELLBUTRIN in approximately 10% of the 2,400 patients and volunteers who participated in
594 clinical trials during the product’s initial development. The more common events causing
595 discontinuation include neuropsychiatric disturbances (3.0%), primarily agitation and
596 abnormalities in mental status; gastrointestinal disturbances (2.1%), primarily nausea and
597 vomiting; neurological disturbances (1.7%), primarily seizures, headaches, and sleep
598 disturbances; and dermatologic problems (1.4%), primarily rashes. It is important to note,
599 however, that many of these events occurred at doses that exceed the recommended daily dose.

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

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

614

615 **Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**
616 **Clinical Trials* (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

617 *Events reported by at least 1% of patients receiving WELLBUTRIN are included.
618

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

627 The following definitions of frequency are used: Frequent adverse events are defined as those
628 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
629 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

667 **Endocrine:** syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia,
668 hypoglycemia

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

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

673 **Musculoskeletal:** arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis, muscle
674 weakness

675 **Nervous:** aggression, coma, delirium, dream abnormalities, paranoid ideation, paresthesia,
676 restlessness, unmasking of tardive dyskinesia

677 **Skin and Appendages:** Stevens-Johnson syndrome, angioedema, exfoliative dermatitis,
678 urticaria

679 **Special Senses:** tinnitus, [increased intraocular pressure](#)

680 DRUG ABUSE AND DEPENDENCE

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

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

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

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

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

700 **OVERDOSAGE**

701 **Human Overdose Experience:** Overdoses of up to 30 g or more of bupropion have been
702 reported. Seizure was reported in approximately one third of all cases. Other serious reactions
703 reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus
704 tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle
705 rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported
706 mainly when bupropion was part of multiple drug overdoses.

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

711 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.
712 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first
713 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.
714 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with
715 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in
716 symptomatic patients.

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

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

724 In managing overdosage, consider the possibility of multiple drug involvement. The physician
725 should consider contacting a poison control center for additional information on the treatment of

726 any overdose. Telephone numbers for certified poison control centers are listed in the
727 *Physicians' Desk Reference* (PDR).

728 **DOSAGE AND ADMINISTRATION**

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

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

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

744

745 **Table 2. 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

746

747 **Increasing the Dosage Above 300 mg/Day:** As with other antidepressants, the full
748 antidepressant effect of WELLBUTRIN may not be evident until 4 weeks of treatment or longer.
749 An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than
750 150 mg each, may be considered for patients in whom no clinical improvement is noted after
751 several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished
752 using the 75- or 100-mg tablets. The 100-mg tablet must be administered 4 times daily with at
753 least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single
754 dose. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate
755 response after an appropriate period of treatment at 450 mg/day.

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

760 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN
761 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should

762 not exceed 75 mg once a day in these patients. WELLBUTRIN should be used with caution in
763 patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced
764 frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis
765 (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

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

769 HOW SUPPLIED

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

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

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

775

776

MEDICATION GUIDE

777

WELLBUTRIN[®] (WELL byu-trin) (bupropion hydrochloride) Tablets

778

779

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

784

785 **IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What**
786 **is the most important information I should know about WELLBUTRIN?” It contains**
787 **important information about this medication. It immediately follows the next section called**
788 **“About Using Antidepressants in Children and Teenagers.”**

789

790

About Using Antidepressants in Children and Teenagers

791

792 **What is the most important information I should know if my child is being prescribed an**
793 **antidepressant?**

794

795 Parents or guardians need to think about 4 important things when their child is prescribed an
796 antidepressant:

797

1. There is a risk of suicidal thoughts or actions

798

2. How to try to prevent suicidal thoughts or actions in your child

799

3. You should watch for certain signs if your child is taking an antidepressant

800

4. There are benefits and risks when using antidepressants

801

802 **1. There is a Risk of Suicidal Thoughts or Actions**

803

804 Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

805

806 Antidepressants increase suicidal thoughts and actions in some children and teenagers. But
807 suicidal thoughts and actions can also be caused by depression, a serious medical condition that
808 is commonly treated with antidepressants. Thinking about killing yourself or trying to kill
809 yourself is called *suicidality* or *being suicidal*.

810

811 A large study combined the results of 24 different studies of children and teenagers with
812 depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an
813 antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients
814 became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4
815 out of every 100 patients became suicidal.

816

817 **For some children and teenagers, the risks of suicidal actions may be especially high.** These
818 include patients with

- 819 • Bipolar illness (sometimes called manic-depressive illness)
- 820 • A family history of bipolar illness
- 821 • A personal or family history of attempting suicide

822 If any of these are present, make sure you tell your healthcare provider before your child takes an
823 antidepressant.

824

825 **2. How to Try to Prevent Suicidal Thoughts and Actions**

826

827 To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her
828 or his moods or actions, especially if the changes occur suddenly. Other important people in your
829 child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers,
830 and other important people). The changes to look out for are listed in Section 3, on what to watch
831 for.

832

833 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.
834 After starting an antidepressant, your child should generally see his or her healthcare provider:

- 835 • Once a week for the first 4 weeks
- 836 • Every 2 weeks for the next 4 weeks
- 837 • After taking the antidepressant for 12 weeks
- 838 • After 12 weeks, follow your healthcare provider's advice about how often to come back
- 839 • More often if problems or questions arise (see Section 3)

840

841 You should call your child’s healthcare provider between visits if needed.

842

843 **3. You Should Watch For Certain Signs if Your Child is Taking an Antidepressant**

844

845 Contact your child’s healthcare provider *right away* if your child exhibits any of the following
846 signs for the first time, or they seem worse, or worry you, your child, or your child’s teacher:

- 847 • Thoughts about suicide or dying
- 848 • Attempts to commit suicide
- 849 • New or worse depression
- 850 • New or worse anxiety
- 851 • Feeling very agitated or restless
- 852 • Panic attacks
- 853 • Difficulty sleeping (insomnia)
- 854 • New or worse irritability
- 855 • Acting aggressive, being angry, or violent
- 856 • Acting on dangerous impulses
- 857 • An extreme increase in activity and talking
- 858 • Other unusual changes in behavior or mood

859

860 Never let your child stop taking an antidepressant without first talking to his or her healthcare
861 provider. Stopping an antidepressant suddenly can cause other symptoms.

862

863 **4. There are Benefits and Risks When Using Antidepressants**

864

865 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses
866 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases
867 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also
868 the risks of not treating it. You and your child should discuss all treatment choices with your
869 healthcare provider, not just the use of antidepressants.

870

871 Other side effects can occur with antidepressants (see section below).

872

873 Of all antidepressants, only fluoxetine (~~Prozac~~PROZAC[®])* has been FDA approved to treat
874 pediatric depression.

875

876 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine
877 (~~Prozac~~PROZAC[®])*, sertraline (~~Zoloft~~ZOLOFT[®])*, fluvoxamine (LUVOX[®])*, and
878 clomipramine (~~Anafranil~~ANAFRANIL[®])*.

879

880 Your healthcare provider may suggest other antidepressants based on the past experience of your
881 child or other family members.

882

883 **Is this all I need to know if my child is being prescribed an antidepressant?**

884

885 No. This is a warning about the risk of suicidality. Other side effects can occur with
886 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the
887 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an
888 antidepressant. Ask your healthcare provider or pharmacist where to find more information.

889

890 ~~*The following are registered trademarks of their respective manufacturers: Prozac[®]/Eli Lilly
891 and Company; Zoloft[®]/Pfizer Pharmaceuticals; Anafranil[®]/Mallinckrodt Inc.~~

892

893 ~~This Medication Guide has been approved by the U.S. Food and Drug Administration for all
894 antidepressants.~~

895

896 ~~January 2005~~ ~~MG-WT:1~~

897

898



899

900 ~~Manufactured by~~
901 ~~DSM Pharmaceuticals, Inc.~~
902 ~~Greenville, NC 27834 for~~
903 ~~GlaxoSmithKline~~
904 ~~Research Triangle Park, NC 27709~~

905

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907

908 ~~May 2006~~ ~~RL-2281~~

909

910

**~~PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT. ALSO
PROVIDE AN APPROVED MEDICATION GUIDE ABOUT USING
ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS.~~**

911

912

913

914

915

Patient Information
WELLBUTRIN[®]-(WELL-byu-trin)
(bupropion hydrochloride) Tablets

916
917 ~~Read the Patient Information that comes with WELLBUTRIN before you start taking~~
918 ~~WELLBUTRIN and each time you get a refill. There may be new information. This leaflet~~
919 ~~does not take the place of talking with your doctor about your medical condition or your~~
920 ~~treatment.~~

921

922 **What is the most important information I should know about WELLBUTRIN?**

923

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

- 926 • with certain medical problems.
927 • who take certain medicines.

928

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

934

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

937

938 **What is important information I should know and share with my family about taking**
939 **antidepressants?**

940 Patients and their families should watch out for worsening depression or thoughts of suicide.
941 Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated,
942 panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and
943 hyperactive, not being able to sleep or other unusual changes in behavior. If this happens,
944 especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.
945 ~~A patient Medication Guide will be provided to you with each prescription of WELLBUTRIN~~
946 ~~For additional information, see section above~~ entitled "About Using Antidepressants in Children
947 and Teenagers." WELLBUTRIN has not been studied in children under the age of 18 and is not
948 approved for the use in children and teenagers.

949

950 **What is WELLBUTRIN?**

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

953

954 **Who should not take WELLBUTRIN?**

955 **Do not take WELLBUTRIN if you**

- 956 • have or had a seizure disorder or epilepsy.
957 • **are taking ZYBAN (used to help people stop smoking) or any other medicines that**
958 **contain bupropion hydrochloride, such as WELLBUTRIN SR Sustained-Release**

959 **Tablets or WELLBUTRIN XL Extended-Release Tablets.** Bupropion is the same
960 ingredient that is in WELLBUTRIN.

- 961 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these
962 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 963 • have taken within the last 14 days medicine for depression called a monoamine oxidase
964 inhibitor (MAOI), such as NARDIL^{®*} (phenelzine sulfate), PARNATE[®] (tranylcypromine
965 sulfate), or MARPLAN^{®*} (isocarboxazid).
- 966 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 967 • are allergic to the active ingredient in WELLBUTRIN, bupropion, or to any of the inactive
968 ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN.

969

970 **What should I tell my doctor before using WELLBUTRIN?**

- 971 • **Tell your doctor about your medical conditions.** Tell your doctor if you:
 - 972 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN can harm
973 your unborn baby. If you can use WELLBUTRIN while you are pregnant, talk to your
974 doctor about how you can be on the Bupropion Pregnancy Registry.
 - 975 • **are breastfeeding.** WELLBUTRIN passes through your milk. It is not known if
976 WELLBUTRIN can harm your baby.
 - 977 • **have liver problems,** especially cirrhosis of the liver.
 - 978 • have kidney problems.
 - 979 • have an eating disorder, such as anorexia nervosa or bulimia.
 - 980 • have had a head injury.
 - 981 • have had a seizure (convulsion, fit).
 - 982 • have a tumor in your nervous system (brain or spine).
 - 983 • have had a heart attack, heart problems, or high blood pressure.
 - 984 • are a diabetic taking insulin or other medicines to control your blood sugar.
 - 985 • drink a lot of alcohol.
 - 986 • abuse prescription medicines or street drugs.
- 987 • **Tell your doctor about all the medicines you take,** including prescription and non-
988 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
989 chances of having seizures or other serious side effects if you take them while you are using
990 WELLBUTRIN.

991

992 ~~WELLBUTRIN has not been studied in children under the age of 18 years.~~

993

994 **How should I take WELLBUTRIN?**

- 995 • Take WELLBUTRIN exactly as prescribed by your doctor.
- 996 • Take WELLBUTRIN at the same time each day.
- 997 • Take your doses of WELLBUTRIN at least 6 hours apart.
- 998 • You may take WELLBUTRIN with or without food.

- 999 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
1000 take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN
1001 can increase your chance of having a seizure.
- 1002 • If you take too much WELLBUTRIN, or overdose, call your local emergency room or poison
1003 control center right away.
- 1004 • **Do not take any other medicines while using WELLBUTRIN unless your doctor has**
1005 **told you it is okay.**
- 1006 • It may take several weeks for you to feel that WELLBUTRIN is working. Once you feel
1007 better, it is important to keep taking WELLBUTRIN exactly as directed by your doctor. Call
1008 your doctor if you do not feel WELLBUTRIN is working for you.
- 1009 • Do not change your dose or stop taking WELLBUTRIN without talking with your doctor
1010 first.
- 1011

1012 **What should I avoid while taking WELLBUTRIN?**

- 1013 • Do not drink a lot of alcohol while taking WELLBUTRIN. If you usually drink a lot of
1014 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking
1015 alcohol, you may increase your risk of having seizures.
- 1016 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN affects you.
1017 WELLBUTRIN can impair your ability to perform these tasks.
- 1018

1019 **What are possible side effects of WELLBUTRIN?**

- 1020 • **Seizures.** Some patients get seizures while taking WELLBUTRIN. **If you have a seizure**
1021 **while taking WELLBUTRIN, stop taking the tablets and call your doctor right away.**
1022 Do not take WELLBUTRIN again if you have a seizure.
- 1023 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes
1024 severe, while taking WELLBUTRIN. The chance of high blood pressure may be increased if
1025 you also use nicotine replacement therapy (for example a nicotine patch) to help you stop
1026 smoking.
- 1027 • **Severe allergic reactions. Stop taking WELLBUTRIN and call your doctor right away**
1028 **if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or**
1029 **around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing.** These
1030 could be signs of a serious allergic reaction.
- 1031 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while
1032 taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations
1033 (seeing or hearing things that are not there), paranoia (feeling that people are against you), or
1034 feeling confused. If this happens to you, call your doctor.
- 1035

1036 The most common side effects of WELLBUTRIN are nervousness, constipation, trouble
1037 sleeping, dry mouth, headache, nausea, vomiting, and shakiness (tremor).

1038

1039 If you have nausea, you may want to take your medicine with food. If you have trouble sleeping,
1040 do not take your medicine too close to bedtime.

1041

1042 Tell your doctor right away about any side effects that bother you.

1043

1044 These are not all the side effects of WELLBUTRIN. For a complete list, ask your doctor or
1045 pharmacist.

1046

1047 **How should I store WELLBUTRIN?**

- 1048 • Store WELLBUTRIN at room temperature. Store out of direct sunlight. Keep
1049 WELLBUTRIN in its tightly closed bottle.

1050

1051 **General Information about WELLBUTRIN.**

- 1052 • Medicines are sometimes prescribed for purposes other than those listed in a Medication
1053 Guide-conditions that are not mentioned in patient information leaflets. Do not use
1054 WELLBUTRIN for a condition for which it was not prescribed. Do not give WELLBUTRIN
1055 to other people, even if they have the same symptoms you have. It may harm them. Keep
1056 WELLBUTRIN out of the reach of children.

1057

1058 This leaflet-Medication Guide summarizes important information about WELLBUTRIN. For
1059 more information, talk to your doctor. You can ask your doctor or pharmacist for information
1060 about WELLBUTRIN that is written for health professionals.

1061

1062 **What are the ingredients in WELLBUTRIN?**

1063 Active ingredient: bupropion hydrochloride.

1064

1065 Inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake,
1066 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and
1067 titanium dioxide; 100-mg tablet – FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake,
1068 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and
1069 titanium dioxide.

1070

1071 *The following are registered trademarks of their respective manufacturers: PROZAC[®]/Eli Lilly
1072 and Company; ZOLOFT[®]/Pfizer Pharmaceuticals; LUVOX[®]/Solvay Pharmaceuticals, Inc;
1073 ANAFRANIL[®]/Mallinckrodt Inc; NARDIL[®]/Warner Lambert Company;
1074 Marplan[®]/Oxford Pharmaceutical Services, Inc.

1075

1076 **R_x only**

1077

1078 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1079

1080 September 2006

MG-WT:2

1081



1082

1083 Manufactured by DSM Pharmaceuticals, Inc.

1084 Greenville, NC 27834 for

1085 GlaxoSmithKline

1086 Research Triangle Park, NC 27709

1087

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1089

1090 ~~May 2006~~September 2006

RL-~~2281~~2293

PRESCRIBING INFORMATION

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

Suicidality in Children and Adolescents

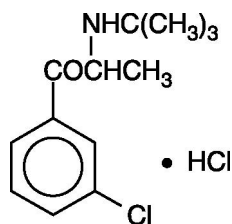
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN SR or any other antidepressant in a child or adolescent must balance this risk with the clinical need.

Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. WELLBUTRIN SR is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

WELLBUTRIN SR (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C₁₃H₁₈ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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

42 **CLINICAL PHARMACOLOGY**

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

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

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

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

68 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been
69 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group
70 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,
71 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome
72 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,
73 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.

74 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of
75 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency
76 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,
77 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is
78 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-
79 fold less potent than bupropion. This may be of clinical importance because the plasma
80 concentrations of the metabolites are as high or higher than those of bupropion.

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

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

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

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

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

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

113 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for
114 bupropion and the other metabolites in the 2 patient groups were minimal.

115 The second study showed no statistically significant differences in the pharmacokinetics of
116 bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis
117 compared to 8 healthy volunteers. However, more variability was observed in some of the
118 pharmacokinetic parameters for bupropion (AUC, C_{max} , and T_{max}) and its active metabolites ($t_{1/2}$)
119 in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic
120 cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by
121 approximately 70% and 3-fold, respectively) and more variable when compared to values in
122 healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with
123 severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion,
124 the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers
125 threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower.
126 The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for
127 threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for
128 hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for
129 hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively,
130 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,
131 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

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

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

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

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

160 **CLINICAL TRIALS**

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

177 Although there are not as yet independent trials demonstrating the antidepressant effectiveness
178 of the sustained-release formulation of bupropion, studies have demonstrated the bioequivalence
179 of the immediate-release and sustained-release forms of bupropion under steady-state conditions,
180 i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 100 mg
181 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and
182 extent of absorption, for parent drug and metabolites.

183 In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder,
184 recurrent type, who had responded during an 8-week open trial on WELLBUTRIN SR (150 mg
185 twice daily) were randomized to continuation of their same WELLBUTRIN SR dose or placebo,
186 for up to 44 weeks of observation for relapse. Response during the open phase was defined as
187 CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final
188 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that
189 drug treatment was needed for worsening depressive symptoms. Patients receiving continued
190 WELLBUTRIN SR treatment experienced significantly lower relapse rates over the subsequent
191 44 weeks compared to those receiving placebo.

192 **INDICATIONS AND USAGE**

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

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

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

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

211 **CONTRAINDICATIONS**

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

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

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

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

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

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

228 **WARNINGS**

229 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),
230 both adult and pediatric, may experience worsening of their depression and/or the emergence of

231 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they
232 are taking antidepressant medications, and this risk may persist until significant remission
233 occurs. There has been a long-standing concern that antidepressants may have a role in inducing
234 worsening of depression and the emergence of suicidality in certain patients. Antidepressants
235 increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children
236 and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

237 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and
238 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of
239 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events
240 representing suicidal behavior or thinking (suicidality) during the first few months of treatment
241 in those receiving antidepressants. The average risk of such events in patients receiving
242 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk
243 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of
244 suicidality was most consistently observed in the MDD trials, but there were signals of risk
245 arising from some trials in other psychiatric indications (obsessive compulsive disorder and
246 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown
247 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several
248 months. It is also unknown whether the suicidality risk extends to adults.

249 **All pediatric patients being treated with antidepressants for any indication should be**
250 **observed closely for clinical worsening, suicidality, and unusual changes in behavior,**
251 **especially during the initial few months of a course of drug therapy, or at times of dose**
252 **changes, either increases or decreases. Such observation would generally include at least**
253 **weekly face-to-face contact with patients or their family members or caregivers during the**
254 **first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at**
255 **12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may**
256 **be appropriate between face-to-face visits.**

257 **Adults with MDD or co-morbid depression in the setting of other psychiatric illness**
258 **being treated with antidepressants should be observed similarly for clinical worsening and**
259 **suicidality, especially during the initial few months of a course of drug therapy, or at times**
260 **of dose changes, either increases or decreases.**

261 **In addition, patients with a history of suicidal behavior or thoughts, those patients**
262 **exhibiting a significant degree of suicidal ideation prior to commencement of treatment,**
263 **and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and**
264 **should receive careful monitoring during treatment.**

265 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility,
266 aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have
267 been reported in adult and pediatric patients being treated with antidepressants for major
268 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.
269 Although a causal link between the emergence of such symptoms and either the worsening of

270 depression and/or the emergence of suicidal impulses has not been established, there is concern
271 that such symptoms may represent precursors to emerging suicidality.

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

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

283 Prescriptions for WELLBUTRIN SR should be written for the smallest quantity of tablets
284 consistent with good patient management, in order to reduce the risk of overdose. Families and
285 caregivers of adults being treated for depression should be similarly advised.

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

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

302
303 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures
304 is also related to patient factors, clinical situations, and concomitant medications, which
305 must be considered in selection of patients for therapy with WELLBUTRIN SR.
306 WELLBUTRIN SR should be discontinued and not restarted in patients who experience a
307 seizure while on treatment.

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

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

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

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

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

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

- 347 • the total daily dose of WELLBUTRIN SR Tablets does *not* exceed 400 mg,

- 348 • the daily dose is administered twice daily, and
- 349 • the rate of incrementation of dose is gradual.
- 350 • No single dose should exceed 200 mg to avoid high peak concentrations of bupropion
- 351 and/or its metabolites.

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

356 **Hepatic Impairment:** WELLBUTRIN SR should be used with extreme caution in patients
357 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,
358 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is
359 likely to occur in such patients to a greater extent than usual. The dose should not exceed
360 100 mg every day or 150 mg every other day in these patients (see CLINICAL
361 PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

366 PRECAUTIONS

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

369

370 **Table 1. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials**

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

371

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

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

377 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Depressed
378 patients treated with an immediate-release formulation of bupropion or with WELLBUTRIN SR
379 Tablets have been reported to show a variety of neuropsychiatric signs and symptoms, including

380 delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some
381 cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

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

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

387

388 **Table 2. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials**

Weight Change	WELLBUTRIN SR 300 mg/day (n = 339)	WELLBUTRIN SR 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

389

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

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

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

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

409 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN[®]
410 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-
411 release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher
412 incidence of treatment-emergent hypertension in patients treated with the combination of
413 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the
414 combination of sustained-release bupropion and NTS had treatment-emergent hypertension

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

421 There is no clinical experience establishing the safety of WELLBUTRIN SR Tablets in
422 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care
423 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed
424 patients who had previously developed orthostatic hypotension while receiving tricyclic
425 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with
426 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine
427 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in
428 2 patients for exacerbation of baseline hypertension.

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

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

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

448 **Information for Patients:** Prescribers or other health professionals should inform patients,
449 their families, and their caregivers about the benefits and risks associated with treatment with
450 WELLBUTRIN SR and should counsel them in its appropriate use. A ~~patient~~ Medication Guide
451 About Using Antidepressants in Children and Teenagers and important information about
452 using is available for WELLBUTRIN SR will be dispensed by the pharmacist with each new
453 prescription and refill of WELLBUTRIN SR. The prescriber or health professional should
454 instruct patients, their families, and their caregivers to read the Medication Guide and should

455 assist them in understanding its contents. Patients should be given the opportunity to discuss the
456 contents of the Medication Guide and to obtain answers to any questions they may have. The
457 complete text of the Medication Guide is reprinted at the end of this document. ~~Additional~~
458 ~~important information concerning WELLBUTRIN SR is provided in a tear-off leaflet entitled~~
459 ~~"Patient Information" at the end of this labeling.~~

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

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

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

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

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

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

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

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

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

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

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

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

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

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

520 Multiple oral doses of bupropion had no statistically significant effects on the single dose
521 pharmacokinetics of lamotrigine in 12 healthy volunteers ~~and was associated with a slight~~
522 ~~increase in the AUC (15%) of lamotrigine glucuronide.~~

523 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
524 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to
525 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.
526 Nevertheless, there may be the potential for clinically important alterations of blood levels of
527 coadministered drugs.

528 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most
529 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are
530 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this
531 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a
532 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6
533 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of
534 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of

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

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

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

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

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

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

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

563 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies
564 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These
565 doses are approximately 7 and 2 times the maximum recommended human dose (MRHD),
566 respectively, on a mg/m² basis. In the rat study there was an increase in nodular proliferative
567 lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a
568 mg/m² basis); lower doses were not tested. The question of whether or not such lesions may be
569 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen
570 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in
571 either study.

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

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

577 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. In studies conducted in rats and
578 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively
579 (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively,
580 on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity
581 was found in either species; however, in rabbits, slightly increased incidences of fetal
582 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,
583 approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal weights were
584 seen at 50 mg/kg and greater.

585 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately
586 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy and lactation,
587 there were no apparent adverse effects on offspring development.

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

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

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

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

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

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

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

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

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

629 **ADVERSE REACTIONS** (See also WARNINGS and PRECAUTIONS.)

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

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

638 **WELLBUTRIN SR Tablets:** In placebo-controlled clinical trials, 9% and 11% of patients
639 treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 4% of patients
640 treated with placebo discontinued treatment due to adverse events. The specific adverse events in
641 these trials that led to discontinuation in at least 1% of patients treated with either 300 or
642 400 mg/day of WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed
643 in Table 3.

644

645 **Table 3. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials**

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

646

647 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**
 648 **Treated With WELLBUTRIN SR Tablets:** Table 4 enumerates treatment-emergent adverse
 649 events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR
 650 Tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or
 651 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo
 652 group are included. Reported adverse events were classified using a COSTART-based
 653 Dictionary.

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

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

665
666

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

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

Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
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%	—
<u>Amblyopia</u> <u>Blurred vision or diplopia</u>	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—

Urinary tract infection	1%	0%	—
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667 * Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day
668 of WELLBUTRIN SR Tablets, but equally or more frequently in the placebo group, were:
669 abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis,
670 dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory
671 disorder, rhinitis, and tooth disorder.

672 † Incidence based on the number of female patients.

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

674

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

676 Adverse events from Table 4 occurring in at least 5% of patients treated with
677 WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed below for the
678 300- and 400-mg/day dose groups.

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

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

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

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

690 Adverse events for which frequencies are provided below occurred in clinical trials with the
691 sustained-release formulation of bupropion. The frequencies represent the proportion of patients
692 who experienced a treatment-emergent adverse event on at least one occasion in
693 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients
694 who experienced an adverse event requiring discontinuation of treatment in an open-label
695 surveillance study with WELLBUTRIN SR Tablets (n = 3,100). All treatment-emergent adverse
696 events are included except those listed in Tables 1 through 4, those events listed in other
697 safety-related sections, those adverse events subsumed under COSTART terms that are either
698 overly general or excessively specific so as to be uninformative, those events not reasonably
699 associated with the use of the drug, and those events that were not serious and occurred in fewer
700 than 2 patients. Events of major clinical importance are described in the WARNINGS and
701 PRECAUTIONS sections of the labeling.

702 Events are further categorized by body system and listed in order of decreasing frequency
703 according to the following definitions of frequency: Frequent adverse events are defined as those

704 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
705 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

728 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed
729 was glycosuria.

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

732 **Nervous System:** Infrequent were abnormal coordination, decreased libido,
733 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
734 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also
735 observed were abnormal electroencephalogram (EEG), akinesia, aggression, aphasia, coma,
736 delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome,
737 hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid
738 ideation, restlessness, and unmasking tardive dyskinesia.

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

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

742 **Special Senses:** Infrequent were accommodation abnormality and dry eye. Also observed
743 were deafness, diplopia, [increased intraocular pressure](#), and mydriasis.

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

747 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

770 **OVERDOSAGE**

771 **Human Overdose Experience:** Overdoses of up to 30 g or more of bupropion have been
772 reported. Seizure was reported in approximately one third of all cases. Other serious reactions
773 reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus
774 tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle
775 rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported
776 mainly when bupropion was part of multiple drug overdoses.

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

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

783 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.
784 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with
785 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in
786 symptomatic patients.

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

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

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

798 **DOSAGE AND ADMINISTRATION**

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

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

808 **Initial Treatment:** The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day,
809 given as 150 mg twice daily. Dosing with WELLBUTRIN SR Tablets should begin at
810 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately
811 tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made
812 as early as day 4 of dosing. There should be an interval of at least 8 hours between successive
813 doses.

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

819 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require
820 several months or longer of sustained pharmacological therapy beyond response to the acute
821 episode. In a study in which patients with major depressive disorder, recurrent type, who had

822 responded during 8 weeks of acute treatment with WELLBUTRIN SR were assigned randomly
823 to placebo or to the same dose of WELLBUTRIN SR (150 mg twice daily) during 44 weeks of
824 maintenance treatment as they had received during the acute stabilization phase, longer-term
825 efficacy was demonstrated (see CLINICAL TRIALS under CLINICAL PHARMACOLOGY).
826 Based on these limited data, it is unknown whether or not the dose of WELLBUTRIN SR needed
827 for maintenance treatment is identical to the dose needed to achieve an initial response. Patients
828 should be periodically reassessed to determine the need for maintenance treatment and the
829 appropriate dose for such treatment.

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

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

840 **HOW SUPPLIED**

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

844 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are
845 purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of
846 60 (NDC 0173-0135-55) tablets.

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

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

852

853

MEDICATION GUIDE

854

WELLBUTRIN SR[®] (WELL byu-trin)

855

(bupropion hydrochloride) Sustained-Release Tablets

856

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

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IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What is the most important information I should know about WELLBUTRIN SR?” It contains important information about this medication. It immediately follows the next section called “About Using Antidepressants in Children and Teenagers.”

About Using Antidepressants in Children and Teenagers

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenager sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

901

902 **2. How to Try to Prevent Suicidal Thoughts and Actions**

903

904 To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her
905 or his moods or actions, especially if the changes occur suddenly. Other important people in your
906 child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers,
907 and other important people). The changes to look out for are listed in Section 3, on what to watch
908 for.

909

910 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

911 After starting an antidepressant, your child should generally see his or her healthcare provider:

912

- Once a week for the first 4 weeks

913

- Every 2 weeks for the next 4 weeks

914

- After taking the antidepressant for 12 weeks

915

- After 12 weeks, follow your healthcare provider's advice about how often to come back

916

- More often if problems or questions arise (see Section 3)

917

918 You should call your child's healthcare provider between visits if needed.

919

920 **3. You Should Watch For Certain Signs if Your Child is Taking an Antidepressant**

921

922 Contact your child's healthcare provider *right away* if your child exhibits any of the following
923 signs for the first time, or they seem worse, or worry you, your child, or your child's teacher:

924

- Thoughts about suicide or dying

925

- Attempts to commit suicide

926

- New or worse depression

927

- New or worse anxiety

928

- Feeling very agitated or restless

929

- Panic attacks

930

- Difficulty sleeping (insomnia)

931

- New or worse irritability

932

- Acting aggressive, being angry, or violent

933

- Acting on dangerous impulses

934

- An extreme increase in activity and talking

935

- Other unusual changes in behavior or mood

936

937 Never let your child stop taking an antidepressant without first talking to his or her healthcare
938 provider. Stopping an antidepressant suddenly can cause other symptoms.

939

940 **4. There are Benefits and Risks When Using Antidepressants**

941

942 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses
943 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases
944 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also
945 the risks of not treating it. You and your child should discuss all treatment choices with your
946 healthcare provider, not just the use of antidepressants.

947

948 Other side effects can occur with antidepressants (see section below).

949

950 Of all antidepressants, only fluoxetine (~~Prozac~~PROZAC[®])* has been FDA approved to treat
951 pediatric depression.

952

953 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine
954 (~~Prozac~~PROZAC[®])*, sertraline (~~Zoloft~~ZOLOFT[®])*, fluvoxamine (LUVOX[®])*, and
955 clomipramine (~~Anafranil~~ANAFRANIL[®])*.

956

957 Your healthcare provider may suggest other antidepressants based on the past experience of your
958 child or other family members.

959

960 **Is this all I need to know if my child is being prescribed an antidepressant?**

961

962 No. This is a warning about the risk of suicidality. Other side effects can occur with
963 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the
964 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an
965 antidepressant. Ask your healthcare provider or pharmacist where to find more information.

966

967 ~~*The following are registered trademarks of their respective manufacturers: Prozac[®]/Eli Lilly
968 and Company; Zoloft[®]/Pfizer Pharmaceuticals; Anafranil[®]/Mallinckrodt Inc.~~

969

970 ~~This Medication Guide has been approved by the U.S. Food and Drug Administration for all
971 antidepressants.~~

972

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974



975

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989

~~PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT. ALSO
PROVIDE AN APPROVED MEDICATION GUIDE ABOUT USING
ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS.~~

990

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~~**Patient Information**
WELLBUTRIN SR[®] (WELL-byu-trin)
(bupropion hydrochloride) Sustained-Release Tablets~~

~~Read the Patient Information that comes with WELLBUTRIN SR before you start taking
WELLBUTRIN SR and each time you get a refill. There may be new information. This leaflet
does not take the place of talking with your doctor about your medical condition or your
treatment.~~

What is the most important information I should know about WELLBUTRIN SR?

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

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

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

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

1016 **What is important information I should know and share with my family about taking**
1017 **antidepressants?**

1018 Patients and their families should watch out for worsening depression or thoughts of suicide.
1019 Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated,
1020 panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and
1021 hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens,
1022 especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.

1023 ~~A patient Medication Guide will be provided to you with each prescription of~~
1024 ~~WELLBUTRIN SR~~ For additional information, see section above entitled "About Using
1025 Antidepressants in Children and Teenagers." WELLBUTRIN SR has not been studied in
1026 children under the age of 18 and is not approved for use in children and teenagers.

1027

1028 **What is WELLBUTRIN SR?**

1029 WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type of
1030 depression called major depressive disorder.

1031

1032 **Who should not take WELLBUTRIN SR?**

1033 **Do not take WELLBUTRIN SR if you**

- 1034 • have or had a seizure disorder or epilepsy.
- 1035 • **are taking ZYBAN[®] (used to help people stop smoking) or any other medicines that**
1036 **contain bupropion hydrochloride, such as WELLBUTRIN[®] Tablets or WELLBUTRIN**
1037 **XL[®] Extended-Release Tablets.** Bupropion is the same active ingredient that is in
1038 WELLBUTRIN SR.
- 1039 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these
1040 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1041 • have taken within the last 14 days medicine for depression called a monoamine oxidase
1042 inhibitor (MAOI), such as NARDIL^{®*} (phenelzine sulfate), PARNATE[®] (tranylcypromine
1043 sulfate), or MARPLAN^{®*} (isocarboxazid).
- 1044 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1045 • are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the
1046 inactive ingredients. See the end of this leaflet for a complete list of ingredients in
1047 WELLBUTRIN SR.

1048

1049 **What should I tell my doctor before using WELLBUTRIN SR?**

- 1050 • **Tell your doctor about your medical conditions. Tell your doctor if you:**
- 1051 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN SR can
1052 harm your unborn baby. If you can use WELLBUTRIN SR while you are pregnant, talk
1053 to your doctor about how you can be on the Bupropion Pregnancy Registry.
- 1054 • **are breastfeeding.** WELLBUTRIN SR passes through your milk. It is not known if
1055 WELLBUTRIN SR can harm your baby.

- 1056 • **have liver problems**, especially cirrhosis of the liver.
- 1057 • have kidney problems.
- 1058 • have an eating disorder such as anorexia nervosa or bulimia.
- 1059 • have had a head injury.
- 1060 • have had a seizure (convulsion, fit).
- 1061 • have a tumor in your nervous system (brain or spine).
- 1062 • have had a heart attack, heart problems, or high blood pressure.
- 1063 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1064 • drink a lot of alcohol.
- 1065 • abuse prescription medicines or street drugs.
- 1066
- 1067 • **Tell your doctor about all the medicines you take**, including prescription and non-
- 1068 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
- 1069 chances of having seizures or other serious side effects if you take them while you are using
- 1070 WELLBUTRIN SR.

1071

1072 ~~WELLBUTRIN SR has not been studied in children under the age of 18 years.~~

1073

1074 **How should I take WELLBUTRIN SR?**

- 1075 • Take WELLBUTRIN SR exactly as prescribed by your doctor.
- 1076 • **Do not chew, cut, or crush WELLBUTRIN SR Tablets.** You must swallow the tablets
- 1077 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 1078 • Take WELLBUTRIN SR at the same time each day.
- 1079 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 1080 • You may take WELLBUTRIN SR with or without food.
- 1081 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
- 1082 take your next tablet at the regular time. **This is very important.** Too much
- 1083 WELLBUTRIN SR can increase your chance of having a seizure.
- 1084 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or
- 1085 poison control center right away.
- 1086 • **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has**
- 1087 **told you it is okay.**
- 1088 • It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel
- 1089 better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor.
- 1090 Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- 1091 • Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor
- 1092 first.

1093

1094 **What should I avoid while taking WELLBUTRIN SR?**

- 1095 • Do not drink a lot of alcohol while taking WELLBUTRIN SR. If you usually drink a lot of
1096 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking
1097 alcohol, you may increase your chance of having seizures.
- 1098 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects
1099 you. WELLBUTRIN SR can impair your ability to perform these tasks.

1100

1101 **What are possible side effects of WELLBUTRIN SR?**

- 1102 • **Seizures.** Some patients get seizures while taking WELLBUTRIN SR. **If you have a seizure**
1103 **while taking WELLBUTRIN SR, stop taking the tablets and call your doctor right**
1104 **away.** Do not take WELLBUTRIN SR again if you have a seizure.
- 1105 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes
1106 severe, while taking WELLBUTRIN SR. The chance of high blood pressure may be
1107 increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help
1108 you stop smoking.
- 1109 • **Severe allergic reactions: Stop taking WELLBUTRIN SR and call your doctor right**
1110 **away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the
1111 mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble
1112 breathing. These could be signs of a serious allergic reaction.
- 1113 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while
1114 taking WELLBUTRIN SR, including delusions (believe you are someone else),
1115 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are
1116 against you), or feeling confused. If this happens to you, call your doctor.

1117

1118 The most common side effects of WELLBUTRIN SR are loss of appetite, dry mouth, skin rash,
1119 sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble
1120 sleeping, muscle pain, nausea, fast heart-beat, sore throat, and urinating more often.

1121

1122 If you have nausea, you may want to take your medicine with food. If you have trouble sleeping,
1123 do not take your medicine too close to bedtime.

1124

1125 Tell your doctor right away about any side effects that bother you.

1126

1127 These are not all the side effects of WELLBUTRIN SR. For a complete list, ask your doctor or
1128 pharmacist.

1129

1130 **How should I store WELLBUTRIN SR?**

- 1131 • Store WELLBUTRIN SR at room temperature. Store out of direct sunlight. Keep
1132 WELLBUTRIN SR in its tightly closed bottle.
- 1133 • WELLBUTRIN SR tablets may have an odor.

1134

1135 **General Information about WELLBUTRIN SR.**

- 1136 • Medicines are sometimes prescribed for purposes other than those listed in a Medication
1137 Guide-conditions that are not mentioned in patient information leaflets. Do not use
1138 WELLBUTRIN SR for a condition for which it was not prescribed. Do not give
1139 WELLBUTRIN SR to other people, even if they have the same symptoms you have. It may
1140 harm them. Keep WELLBUTRIN SR out of the reach of children.

1141

1142 This leaflet-Medication Guide summarizes important information about WELLBUTRIN SR. For
1143 more information, talk with your doctor. You can ask your doctor or pharmacist for information
1144 about WELLBUTRIN SR that is written for health professionals.

1145

1146 **What are the ingredients in WELLBUTRIN SR?**

1147 Active ingredient: bupropion hydrochloride.

1148

1149 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,
1150 microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In
1151 addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C
1152 Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40
1153 Lake. The tablets are printed with edible black ink.

1154

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1156 and Company; ZOLOFT[®]/Pfizer Pharmaceuticals; LUVOX[®]/Solvay Pharmaceuticals, Inc;
1157 ANAFRANIL[®]/Mallinckrodt Inc; NardilNARDIL[®]/Warner Lambert Company;
1158 MarplanMARPLAN[®]/Oxford Pharmaceutical Services, Inc.

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1160 **R_x only**

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1162 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

1163

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