

PRESCRIBING INFORMATION

**WELLBUTRIN<sup>®</sup>**  
**(bupropion hydrochloride)**  
**Tablets**

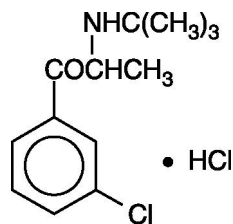
**Suicidality in Children and Adolescents**

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 C<sub>13</sub>H<sub>18</sub>ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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.

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

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

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

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

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

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

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

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

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

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

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

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

109 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was  
110 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in  
111 patients with mild to severe cirrhosis. The first study showed that the half-life of  
112 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in  
113 8 healthy volunteers (32 $\pm$ 14 hours versus 21 $\pm$ 5 hours, respectively). Although not statistically

114 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be  
115 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life  
116 for bupropion and the other metabolites in the 2 patient groups were minimal.

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

134 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
135 renal impairment. The elimination of the major metabolites of bupropion may be reduced by  
136 impaired renal function (see PRECAUTIONS: Renal Impairment).

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

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

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

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

## 158 **INDICATIONS AND USAGE**

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

165 The efficacy of WELLBUTRIN has been established in 3 placebo-controlled trials, including  
166 2 of approximately 3 weeks' duration in depressed inpatients and one of approximately 6 weeks'  
167 duration in depressed outpatients. The depressive disorder of the patients studied corresponds  
168 most closely to the Major Depression category of the APA Diagnostic and Statistical Manual III.

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

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

## 179 **CONTRAINDICATIONS**

180 WELLBUTRIN is contraindicated in patients with a seizure disorder.

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

186 WELLBUTRIN is contraindicated in patients with a current or prior diagnosis of bulimia or  
187 anorexia nervosa because of a higher incidence of seizures noted in such patients treated with  
188 WELLBUTRIN.

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

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

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

## 196 **WARNINGS**

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

205 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and  
206 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of  
207 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events  
208 representing suicidal behavior or thinking (suicidality) during the first few months of treatment  
209 in those receiving antidepressants. The average risk of such events in patients receiving  
210 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk  
211 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of  
212 suicidality was most consistently observed in the MDD trials, but there were signals of risk  
213 arising from some trials in other psychiatric indications (obsessive compulsive disorder and  
214 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown  
215 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several  
216 months. It is also unknown whether the suicidality risk extends to adults.

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

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

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

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

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

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

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

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

264 **Patients should be made aware that WELLBUTRIN contains the same active ingredient**  
265 **found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN**  
266 **should not be used in combination with ZYBAN, or any other medications that contain**  
267 **bupropion, such as WELLBUTRIN SR (bupropion hydrochloride), the sustained-release**

268 formulation or WELLBUTRIN XL (bupropion hydrochloride), the extended-release  
269 formulation.

270

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

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

285 A separate, prospective study was conducted to determine the incidence of seizure  
286 during an 8-week treatment exposure in approximately 3,200 additional patients who  
287 received daily doses of up to 450 mg. Patients were permitted to continue treatment beyond  
288 8 weeks if clinically indicated. Eight seizures occurred during the initial 8-week treatment  
289 period and 5 seizures were reported in patients continuing treatment beyond 8 weeks,  
290 resulting in a total seizure incidence of 0.4%.

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

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

- 299 • **Patient factors:** Predisposing factors that may increase the risk of seizure with  
300 bupropion use include history of head trauma or prior seizure, central nervous system  
301 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications  
302 that lower seizure threshold.
- 303 • **Clinical situations:** Circumstances associated with an increased seizure risk include,  
304 among others, excessive use of alcohol or sedatives (including benzodiazepines);  
305 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and  
306 anorectics; and diabetes treated with oral hypoglycemics or insulin.

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

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

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

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

320 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients  
321 with severe hepatic cirrhosis. In these patients a reduced dose and/or frequency is required,  
322 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is  
323 likely to occur in such patients to a greater extent than usual. The dose should not exceed  
324 75 mg once a day in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS,  
325 and DOSAGE AND ADMINISTRATION).

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

## 330 PRECAUTIONS

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

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

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

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

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

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

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

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

380 There is no clinical experience establishing the safety of WELLBUTRIN in patients with a  
381 recent history of myocardial infarction or unstable heart disease. Therefore, care should be  
382 exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who  
383 had previously developed orthostatic hypotension while receiving tricyclic antidepressants and

384 was also generally well tolerated in a group of 36 depressed inpatients with stable congestive  
385 heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in  
386 the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for  
387 exacerbation of baseline hypertension.

388 **Hepatic Impairment:** WELLBUTRIN should be used with extreme caution in patients with  
389 severe hepatic cirrhosis. In these patients, a reduced dose and frequency is required.

390 WELLBUTRIN should be used with caution in patients with hepatic impairment (including mild  
391 to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in  
392 patients with mild to moderate hepatic cirrhosis.

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

396 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
397 patients with renal impairment. Bupropion is extensively metabolized in the liver to active  
398 metabolites, which are further metabolized and subsequently excreted by the kidneys.  
399 WELLBUTRIN should be used with caution in patients with renal impairment and a reduced  
400 frequency and/or dose should be considered as the metabolites of bupropion may accumulate in  
401 such patients to a greater extent than usual. The patient should be closely monitored for possible  
402 adverse effects that could indicate high drug or metabolite levels.

403 **Information for Patients:** Prescribers or other health professionals should inform patients,  
404 their families, and their caregivers about the benefits and risks associated with treatment with  
405 WELLBUTRIN and should counsel them in its appropriate use. A patient Medication Guide  
406 About Using Antidepressants in Children and Teenagers is available for WELLBUTRIN. The  
407 prescriber or health professional should instruct patients, their families, and their caregivers to  
408 read the Medication Guide and should assist them in understanding its contents. Patients should  
409 be given the opportunity to discuss the contents of the Medication Guide and to obtain answers  
410 to any questions they may have. The complete text of the Medication Guide is reprinted at the  
411 end of this document. Additional important information concerning WELLBUTRIN is provided  
412 in a tear-off leaflet entitled "Patient Information" at the end of this labeling.

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

415 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers  
416 should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,  
417 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),  
418 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal  
419 ideation, especially early during antidepressant treatment and when the dose is adjusted up or  
420 down. Families and caregivers of patients should be advised to observe for the emergence of  
421 such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be  
422 reported to the patient's prescriber or health professional, especially if they are severe, abrupt in  
423 onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be

424 associated with an increased risk for suicidal thinking and behavior and indicate a need for very  
425 close monitoring and possibly changes in the medication.

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

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

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

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

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

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

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

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

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

452 Because bupropion is extensively metabolized, the coadministration of other drugs may affect  
453 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to  
454 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
455 interaction between WELLBUTRIN and drugs that are the substrates or inhibitors of the  
456 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro  
457 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
458 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
459 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
460 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant  
461 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites  
462 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg  
463 sustained-release tablets with and without 800 mg of cimetidine, the pharmacokinetics of  
464 bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases

465 in the AUC and  $C_{max}$ , respectively, of the combined moieties of threohydrobupropion and  
466 erythrohydrobupropion.

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

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

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

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

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

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

498 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
499 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
500 Administration of WELLBUTRIN Tablets to patients receiving either levodopa or amantadine  
501 concurrently should be undertaken with caution, using small initial doses and small gradual dose  
502 increases.

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

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

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

512 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies  
513 were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. In the rat  
514 study there was an increase in nodular proliferative lesions of the liver at doses of 100 to  
515 300 mg/kg/day; lower doses were not tested. The question of whether or not such lesions may be  
516 precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen  
517 in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in  
518 either study.

519 Bupropion produced a borderline positive response (2 to 3 times control mutation rate) in  
520 some strains in the Ames bacterial mutagenicity test, and a high oral dose (300 mg/kg, but not  
521 100 or 200 mg/kg) produced a low incidence of chromosomal aberrations in rats. The relevance  
522 of these results in estimating the risk of human exposure to therapeutic doses is unknown.

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

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

533 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
534 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
535 there were no apparent adverse effects on offspring development.

536 One study has been conducted in pregnant women. This retrospective, managed-care database  
537 study assessed the risk of congenital malformations overall, and cardiovascular malformations  
538 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
539 malformations following exposure to other antidepressants in the first trimester and bupropion  
540 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
541 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
542 showed no greater risk for congenital malformations overall, or cardiovascular malformations  
543 specifically, following first trimester bupropion exposure compared to exposure to all other  
544 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of  
545 this study have not been corroborated. WELLBUTRIN should be used during pregnancy only if  
546 the potential benefit justifies the potential risk to the fetus.

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

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

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

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

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

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

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

577

## 578 **ADVERSE REACTIONS** (see also WARNINGS and PRECAUTIONS)

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

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

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

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

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

603

604 **Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
605 **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

606 \*Events reported by at least 1% of patients receiving WELLBUTRIN are included.

607

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

616 The following definitions of frequency are used: Frequent adverse events are defined as those  
617 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
618 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

656 **Endocrine:** syndrome of inappropriate antidiuretic hormone secretion, hyperglycemia,  
657 hypoglycemia

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

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

662 **Musculoskeletal:** arthralgia, myalgia, muscle rigidity/fever/rhabdomyolysis, muscle  
663 weakness

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

666 **Skin and Appendages:** Stevens-Johnson syndrome, angioedema, exfoliative dermatitis,  
667 urticaria

668 **Special Senses:** tinnitus

## 669 **DRUG ABUSE AND DEPENDENCE**

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

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

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

683 **Animals:** Studies in rodents have shown that bupropion exhibits some pharmacologic actions  
684 common to psychostimulants including increases in locomotor activity and the production of a  
685 mild stereotyped behavior and increases in rates of responding in several schedule-controlled

686 behavior paradigms. Drug discrimination studies in rats showed stimulus generalization between  
687 bupropion and amphetamine and other psychostimulants. Rhesus monkeys have been shown to  
688 self-administer bupropion intravenously.

## 689 **OVERDOSAGE**

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

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

700 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
701 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
702 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
703 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
704 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
705 symptomatic patients.

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

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

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

## 717 **DOSAGE AND ADMINISTRATION**

718 **General Dosing Considerations:** It is particularly important to administer WELLBUTRIN  
719 in a manner most likely to minimize the risk of seizure (see WARNINGS). Increases in dose  
720 should not exceed 100 mg/day in a 3-day period. Gradual escalation in dosage is also important  
721 if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are  
722 to be minimized. If necessary, these effects may be managed by temporary reduction of dose or  
723 the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative  
724 hypnotic usually is not required beyond the first week of treatment. Insomnia may also be

725 minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation  
726 should be stopped.

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

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

733  
734

**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

735

736 **Increasing the Dosage Above 300 mg/Day:** As with other antidepressants, the full  
737 antidepressant effect of WELLBUTRIN may not be evident until 4 weeks of treatment or longer.  
738 An increase in dosage, up to a maximum of 450 mg/day, given in divided doses of not more than  
739 150 mg each, may be considered for patients in whom no clinical improvement is noted after  
740 several weeks of treatment at 300 mg/day. Dosing above 300 mg/day may be accomplished  
741 using the 75- or 100-mg tablets. The 100-mg tablet must be administered 4 times daily with at  
742 least 4 hours between successive doses, in order not to exceed the limit of 150 mg in a single  
743 dose. WELLBUTRIN should be discontinued in patients who do not demonstrate an adequate  
744 response after an appropriate period of treatment at 450 mg/day.

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

749 **Dosage Adjustment for Patients with Impaired Hepatic Function:** WELLBUTRIN  
750 should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should  
751 not exceed 75 mg once a day in these patients. WELLBUTRIN should be used with caution in  
752 patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced  
753 frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis  
754 (see CLINICAL PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

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

## 758 HOW SUPPLIED

759 WELLBUTRIN Tablets, 75 mg of bupropion hydrochloride, are yellow-gold, round, biconvex  
760 tablets printed with "WELLBUTRIN 75" in bottles of 100 (NDC 0173-0177-55).

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

763 **Store at 15° to 25°C (59° to 77°F). Protect from light and moisture.**  
764

## 765 **Medication Guide**

### 766 **WELLBUTRIN<sup>®</sup> (WELL byu-trin)** 767 **(bupropion hydrochloride) Tablets**

#### 768 **About Using Antidepressants in Children and Teenagers**

769

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

772

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

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

779

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

781

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

783

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

788

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

794

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

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

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

802

## 803 **2. How to Try to Prevent Suicidal Thoughts and Actions**

804

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

810

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

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

813

- Once a week for the first 4 weeks

814

- Every 2 weeks for the next 4 weeks

815

- After taking the antidepressant for 12 weeks

816

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

817

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

818

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

820

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

822

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

825

- Thoughts about suicide or dying

826

- Attempts to commit suicide

827

- New or worse depression

828

- New or worse anxiety

829

- Feeling very agitated or restless

830

- Panic attacks

831

- Difficulty sleeping (insomnia)

832

- New or worse irritability

833

- Acting aggressive, being angry, or violent

834

- Acting on dangerous impulses

835

- An extreme increase in activity and talking

836

- Other unusual changes in behavior or mood

837

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

840

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

842

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

848

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

850

851 Of all antidepressants, only fluoxetine (Prozac®)\* has been FDA approved to treat pediatric  
852 depression.

853

854 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine  
855 (Prozac®)\*, sertraline (Zoloft®)\*, fluvoxamine, and clomipramine (Anafranil®)\*.

856

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

859

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

861

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

866

867 \*The following are registered trademarks of their respective manufacturers: Prozac®/Eli Lilly  
868 and Company; Zoloft®/Pfizer Pharmaceuticals; Anafranil®/Mallinckrodt Inc.

869

870 This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
871 antidepressants.

872

873 January 2005

MG-WT:1

874

875



876

877 Manufactured by

878 DSM Pharmaceuticals, Inc.



918 panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and  
919 hyperactive, not being able to sleep or other unusual changes in behavior. If this happens,  
920 especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.  
921 A patient Medication Guide will be provided to you with each prescription of WELLBUTRIN  
922 entitled "About Using Antidepressants in Children and Teenagers." WELLBUTRIN is not  
923 approved for the use in children and teenagers.

#### 924 925 **What is WELLBUTRIN?**

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

#### 928 929 **Who should not take WELLBUTRIN?**

##### 930 **Do not take WELLBUTRIN if you**

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

#### 944 945 **What should I tell my doctor before using WELLBUTRIN?**

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

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

966  
967       WELLBUTRIN has not been studied in children under the age of 18 years.

#### 968 969       **How should I take WELLBUTRIN?**

- 970       • Take WELLBUTRIN exactly as prescribed by your doctor.  
971       • Take WELLBUTRIN at the same time each day.  
972       • Take your doses of WELLBUTRIN at least 6 hours apart.  
973       • You may take WELLBUTRIN with or without food.  
974       • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and  
975       take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN  
976       can increase your chance of having a seizure.  
977       • If you take too much WELLBUTRIN, or overdose, call your local emergency room or poison  
978       control center right away.  
979       • **Do not take any other medicines while using WELLBUTRIN unless your doctor has**  
980       **told you it is okay.**  
981       • It may take several weeks for you to feel that WELLBUTRIN is working. Once you feel  
982       better, it is important to keep taking WELLBUTRIN exactly as directed by your doctor. Call  
983       your doctor if you do not feel WELLBUTRIN is working for you.  
984       • Do not change your dose or stop taking WELLBUTRIN without talking with your doctor  
985       first.

#### 986 987       **What should I avoid while taking WELLBUTRIN?**

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

#### 993 994       **What are possible side effects of WELLBUTRIN?**

- 995       • **Seizures.** Some patients get seizures while taking WELLBUTRIN. **If you have a seizure**  
996       **while taking WELLBUTRIN, stop taking the tablets and call your doctor right away.**  
997       Do not take WELLBUTRIN again if you have a seizure.  
998       • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
999       severe, while taking WELLBUTRIN. The chance of high blood pressure may be increased if

1000 you also use nicotine replacement therapy (for example a nicotine patch) to help you stop  
1001 smoking.

- 1002 • **Severe allergic reactions. Stop taking WELLBUTRIN and call your doctor right away**  
1003 if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or  
1004 around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These  
1005 could be signs of a serious allergic reaction.
- 1006 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1007 taking WELLBUTRIN, including delusions (believe you are someone else), hallucinations  
1008 (seeing or hearing things that are not there), paranoia (feeling that people are against you), or  
1009 feeling confused. If this happens to you, call your doctor.

1010

1011 The most common side effects of WELLBUTRIN are nervousness, constipation, trouble  
1012 sleeping, dry mouth, headache, nausea, vomiting, and shakiness (tremor).

1013

1014 If you have nausea, you may want to take your medicine with food. If you have trouble sleeping,  
1015 do not take your medicine too close to bedtime.

1016

1017 Tell your doctor right away about any side effects that bother you.

1018

1019 These are not all the side effects of WELLBUTRIN. For a complete list, ask your doctor or  
1020 pharmacist.

1021

#### 1022 **How should I store WELLBUTRIN?**

- 1023 • Store WELLBUTRIN at room temperature. Store out of direct sunlight. Keep  
1024 WELLBUTRIN in its tightly closed bottle.

1025

#### 1026 **General Information about WELLBUTRIN.**

- 1027 • Medicines are sometimes prescribed for conditions that are not mentioned in patient  
1028 information leaflets. Do not use WELLBUTRIN for a condition for which it was not  
1029 prescribed. Do not give WELLBUTRIN to other people, even if they have the same  
1030 symptoms you have. It may harm them. Keep WELLBUTRIN out of the reach of children.

1031

1032 This leaflet summarizes important information about WELLBUTRIN. For more information,  
1033 talk to your doctor. You can ask your doctor or pharmacist for information about  
1034 WELLBUTRIN that is written for health professionals.

1035

#### 1036 **What are the ingredients in WELLBUTRIN?**

1037 Active ingredient: bupropion hydrochloride.

1038

1039 Inactive ingredients: 75-mg tablet – D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake,  
1040 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and

1041 titanium dioxide; 100-mg tablet – FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake,  
1042 hydroxypropyl cellulose, hypromellose, microcrystalline cellulose, polyethylene glycol, talc, and  
1043 titanium dioxide.

1044

1045 \*The following are registered trademarks of their respective manufacturers: Nardil<sup>®</sup>/Warner  
1046 Lambert Company; Marplan<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

1047

1048 **R<sub>x</sub> only**

1049



1050

1051 Manufactured by DSM Pharmaceuticals, Inc.

1052 Greenville, NC 27834 for

1053 GlaxoSmithKline

1054 Research Triangle Park, NC 27709

1055

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1057

1058 May 2006

RL-2281

PRESCRIBING INFORMATION

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

**Suicidality in Children and Adolescents**

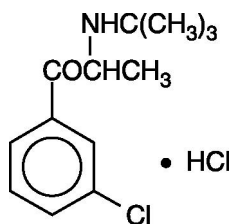
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN SR or any other antidepressant in a child or adolescent must 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 C<sub>13</sub>H<sub>18</sub>ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



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. While the  
45 mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that  
46 this action is mediated by noradrenergic and/or dopaminergic mechanisms.

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

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

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

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

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

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

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

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

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

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

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

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

131 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
132 renal impairment. The elimination of the major metabolites of bupropion may be reduced by  
133 impaired renal function (see PRECAUTIONS: Renal Impairment).

134 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in  
135 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on  
136 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed,  
137 compared to healthy volunteers.

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

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

150 **Smokers:** The effects of cigarette smoking on the pharmacokinetics of bupropion were  
151 studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17  
152 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there

153 was no statistically significant difference in  $C_{max}$ , half-life,  $T_{max}$ , AUC, or clearance of bupropion  
154 or its active metabolites between smokers and nonsmokers.

## 155 **CLINICAL TRIALS**

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

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

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

## 187 **INDICATIONS AND USAGE**

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

189 The efficacy of bupropion in the treatment of a major depressive episode was established in  
190 two 4-week controlled trials of depressed inpatients and in one 6-week controlled trial of  
191 depressed outpatients whose diagnoses corresponded most closely to the Major Depression

192 category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL  
193 PHARMACOLOGY).

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

201 The efficacy of WELLBUTRIN SR in maintaining an antidepressant response for up to  
202 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial  
203 (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use  
204 WELLBUTRIN SR for extended periods should periodically reevaluate the long-term usefulness  
205 of the drug for the individual patient.

## 206 **CONTRAINDICATIONS**

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

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

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

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

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

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

## 223 **WARNINGS**

224 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder (MDD),  
225 both adult and pediatric, may experience worsening of their depression and/or the emergence of  
226 suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they  
227 are taking antidepressant medications, and this risk may persist until significant remission  
228 occurs. There has been a long-standing concern that antidepressants may have a role in inducing  
229 worsening of depression and the emergence of suicidality in certain patients. Antidepressants

230 increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children  
231 and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

232 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and  
233 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of  
234 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events  
235 representing suicidal behavior or thinking (suicidality) during the first few months of treatment  
236 in those receiving antidepressants. The average risk of such events in patients receiving  
237 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk  
238 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of  
239 suicidality was most consistently observed in the MDD trials, but there were signals of risk  
240 arising from some trials in other psychiatric indications (obsessive compulsive disorder and  
241 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown  
242 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several  
243 months. It is also unknown whether the suicidality risk extends to adults.

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

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

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

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

267 Consideration should be given to changing the therapeutic regimen, including possibly  
268 discontinuing the medication, in patients whose depression is persistently worse, or who are  
269 experiencing emergent suicidality or symptoms that might be precursors to worsening depression

270 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the  
271 patient's presenting symptoms.

272 **Families and caregivers of pediatric patients being treated with antidepressants for**  
273 **major depressive disorder or other indications, both psychiatric and nonpsychiatric,**  
274 **should be alerted about the need to monitor patients for the emergence of agitation,**  
275 **irritability, unusual changes in behavior, and the other symptoms described above, as well**  
276 **as the emergence of suicidality, and to report such symptoms immediately to health care**  
277 **providers. Such monitoring should include daily observation by families and caregivers.**  
278 Prescriptions for WELLBUTRIN SR should be written for the smallest quantity of tablets  
279 consistent with good patient management, in order to reduce the risk of overdose. Families and  
280 caregivers of adults being treated for depression should be similarly advised.

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

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

297  
298 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures  
299 is also related to patient factors, clinical situations, and concomitant medications, which  
300 must be considered in selection of patients for therapy with WELLBUTRIN SR.

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

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

306 **Data for the immediate-release formulation of bupropion revealed a seizure incidence**  
307 **of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients**  
308 **treated at doses in a range of 300 to 450 mg/day. The 450-mg/day upper limit of this**  
309 **dose range is close to the currently recommended maximum dose of 400 mg/day for**

310 WELLBUTRIN SR Tablets. This seizure incidence (0.4%) may exceed that of other  
311 marketed antidepressants and WELLBUTRIN SR Tablets up to 300 mg/day by as  
312 much as 4-fold. This relative risk is only an approximate estimate because no direct  
313 comparative studies have been conducted.

314 Additional data accumulated for the immediate-release formulation of bupropion  
315 suggested that the estimated seizure incidence increases almost tenfold between 450 and  
316 600 mg/day, which is twice the usual adult dose and one and one-half the maximum  
317 recommended daily dose (400 mg) of WELLBUTRIN SR Tablets. This  
318 disproportionate increase in seizure incidence with dose incrementation calls for  
319 caution in dosing.

320 Data for WELLBUTRIN SR Tablets revealed a seizure incidence of approximately  
321 0.1% (i.e., 3 of 3,100 patients followed prospectively) in patients treated at doses in a  
322 range of 100 to 300 mg/day. It is not possible to know if the lower seizure incidence  
323 observed in this study involving the sustained-release formulation of bupropion  
324 resulted from the different formulation or the lower dose used. However, as noted  
325 above, the immediate-release and sustained-release formulations are bioequivalent with  
326 regard to both rate and extent of absorption during steady state (the most pertinent  
327 condition to estimating seizure incidence), since most observed seizures occur under  
328 steady-state conditions.

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

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

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

347 WELLBUTRIN SR should be administered with extreme caution to patients with a  
348 history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients

349 treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic  
350 steroids, etc.) that lower seizure threshold.

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

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

### 361 **PRECAUTIONS**

362 **General: Agitation and Insomnia:** Patients in placebo-controlled trials with  
363 WELLBUTRIN SR Tablets experienced agitation, anxiety, and insomnia as shown in Table 1.  
364

365 **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%

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

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

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

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

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

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**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%

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

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

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

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

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

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

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

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

432 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
433 patients with renal impairment. Bupropion is extensively metabolized in the liver to active  
434 metabolites, which are further metabolized and subsequently excreted by the kidneys.  
435 WELLBUTRIN SR should be used with caution in patients with renal impairment and a reduced  
436 frequency and/or dose should be considered as the metabolites of bupropion may accumulate in  
437 such patients to a greater extent than usual. The patient should be closely monitored for possible  
438 adverse effects that could indicate high drug or metabolite levels.

439 **Information for Patients:** Prescribers or other health professionals should inform patients,  
440 their families, and their caregivers about the benefits and risks associated with treatment with  
441 WELLBUTRIN SR and should counsel them in its appropriate use. A patient Medication Guide  
442 About Using Antidepressants in Children and Teenagers is available for WELLBUTRIN SR.  
443 The prescriber or health professional should instruct patients, their families, and their caregivers  
444 to read the Medication Guide and should assist them in understanding its contents. Patients  
445 should be given the opportunity to discuss the contents of the Medication Guide and to obtain  
446 answers to any questions they may have. The complete text of the Medication Guide is reprinted  
447 at the end of this document. Additional important information concerning WELLBUTRIN SR is  
448 provided in a tear-off leaflet entitled "Patient Information" at the end of this labeling.

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

451 **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers  
452 should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia,  
453 irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness),  
454 hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal  
455 ideation, especially early during antidepressant treatment and when the dose is adjusted up or

456 down. Families and caregivers of patients should be advised to observe for the emergence of  
457 such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be  
458 reported to the patient's prescriber or health professional, especially if they are severe, abrupt in  
459 onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be  
460 associated with an increased risk for suicidal thinking and behavior and indicate a need for very  
461 close monitoring and possibly changes in the medication.

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

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

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

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

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

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

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

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

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

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

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

496 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro  
497 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
498 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
499 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
500 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant  
501 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites  
502 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg  
503 WELLBUTRIN SR Tablets with and without 800 mg of cimetidine, the pharmacokinetics of  
504 bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases  
505 in the AUC and  $C_{max}$ , respectively, of the combined moieties of threohydrobupropion and  
506 erythrohydrobupropion.

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

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

512 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
513 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to  
514 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.  
515 Nevertheless, there may be the potential for clinically important alterations of blood levels of  
516 coadministered drugs.

517 ***Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):*** Many drugs, including most  
518 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are  
519 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this  
520 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a  
521 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6  
522 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of  
523 50 mg desipramine increased the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of  
524 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the  
525 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6  
526 has not been formally studied.

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

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

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

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

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

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

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

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

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

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

574 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
575 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
576 there were no apparent adverse effects on offspring development.

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

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

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

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

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

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

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

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

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

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

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

627 **WELLBUTRIN SR Tablets:** In placebo-controlled clinical trials, 9% and 11% of patients  
628 treated with 300 and 400 mg/day, respectively, of WELLBUTRIN SR Tablets and 4% of patients  
629 treated with placebo discontinued treatment due to adverse events. The specific adverse events in  
630 these trials that led to discontinuation in at least 1% of patients treated with either 300 or  
631 400 mg/day of WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed  
632 in Table 3.

633

634 **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%

635

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

637 **Treated With WELLBUTRIN SR Tablets:** Table 4 enumerates treatment-emergent adverse  
638 events that occurred among patients treated with 300 and 400 mg/day of WELLBUTRIN SR  
639 Tablets and with placebo in placebo-controlled trials. Events that occurred in either the 300- or  
640 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo  
641 group are included. Reported adverse events were classified using a COSTART-based  
642 Dictionary.

643 Accurate estimates of the incidence of adverse events associated with the use of any drug are  
644 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician

645 judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward  
646 events in the course of usual medical practice where patient characteristics and other factors  
647 differ from those that prevailed in the clinical trials. These incidence figures also cannot be  
648 compared with those obtained from other clinical studies involving related drug products as each  
649 group of drug trials is conducted under a different set of conditions.

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

654  
655

**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%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage <sup>†</sup>	0%	2%	—
Urinary tract infection	1%	0%	—

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

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

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

663

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

665 Adverse events from Table 4 occurring in at least 5% of patients treated with  
666 WELLBUTRIN SR Tablets and at a rate at least twice the placebo rate are listed below for the  
667 300- and 400-mg/day dose groups.

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

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

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

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

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

691 Events are further categorized by body system and listed in order of decreasing frequency  
692 according to the following definitions of frequency: Frequent adverse events are defined as those  
693 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
694 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

717 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed  
718 was glycosuria.

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

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

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

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

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

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

## 736 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

## 759 **OVERDOSAGE**

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

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

770 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
771 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
772 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
773 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
774 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
775 symptomatic patients.

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

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

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

## 787 **DOSAGE AND ADMINISTRATION**

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

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

797 **Initial Treatment:** The usual adult target dose for WELLBUTRIN SR Tablets is 300 mg/day,  
798 given as 150 mg twice daily. Dosing with WELLBUTRIN SR Tablets should begin at  
799 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately  
800 tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made  
801 as early as day 4 of dosing. There should be an interval of at least 8 hours between successive  
802 doses.

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

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

817 should be periodically reassessed to determine the need for maintenance treatment and the  
818 appropriate dose for such treatment.

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

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

## 829 HOW SUPPLIED

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

833 WELLBUTRIN SR Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are  
834 purple, round, biconvex, film-coated tablets printed with "WELLBUTRIN SR 150" in bottles of  
835 60 (NDC 0173-0135-55) tablets.

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

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

841

842

## Medication Guide

843

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

844

### (bupropion hydrochloride) Sustained-Release Tablets

845

### About Using Antidepressants in Children and Teenagers

846

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

849

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

852

1. There is a risk of suicidal thoughts or actions

853

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

854

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

855

4. There are benefits and risks when using antidepressants

856

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

858

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

860

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

865

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

871

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

- 874
- 875 • Bipolar illness (sometimes called manic-depressive illness)
  - 876 • A family history of bipolar illness
  - 877 • A personal or family history of attempting suicide

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

880

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

882

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

888

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

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

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

895

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

897

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

899

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

- 902 • Thoughts about suicide or dying
- 903 • Attempts to commit suicide
- 904 • New or worse depression
- 905 • New or worse anxiety
- 906 • Feeling very agitated or restless
- 907 • Panic attacks
- 908 • Difficulty sleeping (insomnia)
- 909 • New or worse irritability
- 910 • Acting aggressive, being angry, or violent
- 911 • Acting on dangerous impulses
- 912 • An extreme increase in activity and talking
- 913 • Other unusual changes in behavior or mood

914

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

917

### 918 **4. There are Benefits and Risks When Using Antidepressants**

919

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

925

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

927

928 Of all antidepressants, only fluoxetine (Prozac<sup>®</sup>)\* has been FDA approved to treat pediatric  
929 depression.

930

931 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine  
932 (Prozac<sup>®</sup>)\*, sertraline (Zoloft<sup>®</sup>)\*, fluvoxamine, and clomipramine (Anafranil<sup>®</sup>)\*.

933

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

936

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

938

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

943

944 \*The following are registered trademarks of their respective manufacturers: Prozac<sup>®</sup>/Eli Lilly  
945 and Company; Zoloft<sup>®</sup>/Pfizer Pharmaceuticals; Anafranil<sup>®</sup>/Mallinckrodt Inc.

946

947 This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
948 antidepressants.

949

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960

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961

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962

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

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967

968

**Patient Information**

969

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

970

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

971

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

976

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

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

- 980 • with certain medical problems.
- 981 • who take certain medicines.

982

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

988

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

991

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

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

999 A patient Medication Guide will be provided to you with each prescription of

1000 WELLBUTRIN SR entitled "About Using Antidepressants in Children and Teenagers."

1001 WELLBUTRIN SR is not approved for use in children and teenagers.

1002

1003 **What is WELLBUTRIN SR?**

1004 WELLBUTRIN SR is a prescription medicine used to treat adults with a certain type of  
1005 depression called major depressive disorder.

1006

1007 **Who should not take WELLBUTRIN SR?**

1008 **Do not take WELLBUTRIN SR if you**

- 1009 • have or had a seizure disorder or epilepsy.
- 1010 • **are taking ZYBAN<sup>®</sup> (used to help people stop smoking) or any other medicines that**  
1011 **contain bupropion hydrochloride, such as WELLBUTRIN<sup>®</sup> Tablets or WELLBUTRIN**

1012 **XL<sup>®</sup> Extended-Release Tablets.** Bupropion is the same active ingredient that is in  
1013 WELLBUTRIN SR.

- 1014 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
1015 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1016 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
1017 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
1018 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 1019 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1020 • are allergic to the active ingredient in WELLBUTRIN SR, bupropion, or to any of the  
1021 inactive ingredients. See the end of this leaflet for a complete list of ingredients in  
1022 WELLBUTRIN SR.

1023

#### 1024 **What should I tell my doctor before using WELLBUTRIN SR?**

##### 1025 • **Tell your doctor about your medical conditions. Tell your doctor if you:**

- 1026 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN SR can  
1027 harm your unborn baby. If you can use WELLBUTRIN SR while you are pregnant, talk  
1028 to your doctor about how you can be on the Bupropion Pregnancy Registry.
- 1029 • **are breastfeeding.** WELLBUTRIN SR passes through your milk. It is not known if  
1030 WELLBUTRIN SR can harm your baby.
- 1031 • **have liver problems,** especially cirrhosis of the liver.
- 1032 • have kidney problems.
- 1033 • have an eating disorder such as anorexia nervosa or bulimia.
- 1034 • have had a head injury.
- 1035 • have had a seizure (convulsion, fit).
- 1036 • have a tumor in your nervous system (brain or spine).
- 1037 • have had a heart attack, heart problems, or high blood pressure.
- 1038 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1039 • drink a lot of alcohol.
- 1040 • abuse prescription medicines or street drugs.

1041

- 1042 • **Tell your doctor about all the medicines you take,** including prescription and non-  
1043 prescription medicines, vitamins, and herbal supplements. Many medicines increase your  
1044 chances of having seizures or other serious side effects if you take them while you are using  
1045 WELLBUTRIN SR.

1046

1047 WELLBUTRIN SR has not been studied in children under the age of 18 years.

1048

#### 1049 **How should I take WELLBUTRIN SR?**

- 1050 • Take WELLBUTRIN SR exactly as prescribed by your doctor.

- 1051 • **Do not chew, cut, or crush WELLBUTRIN SR Tablets.** You must swallow the tablets  
1052 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 1053 • Take WELLBUTRIN SR at the same time each day.
- 1054 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 1055 • You may take WELLBUTRIN SR with or without food.
- 1056 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and  
1057 take your next tablet at the regular time. **This is very important.** Too much  
1058 WELLBUTRIN SR can increase your chance of having a seizure.
- 1059 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or  
1060 poison control center right away.
- 1061 • **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has**  
1062 **told you it is okay.**
- 1063 • It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel  
1064 better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor.  
1065 Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- 1066 • Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor  
1067 first.
- 1068

1069 **What should I avoid while taking WELLBUTRIN SR?**

- 1070 • Do not drink a lot of alcohol while taking WELLBUTRIN SR. If you usually drink a lot of  
1071 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking  
1072 alcohol, you may increase your chance of having seizures.
- 1073 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN SR affects  
1074 you. WELLBUTRIN SR can impair your ability to perform these tasks.
- 1075

1076 **What are possible side effects of WELLBUTRIN SR?**

- 1077 • **Seizures.** Some patients get seizures while taking WELLBUTRIN SR. **If you have a seizure**  
1078 **while taking WELLBUTRIN SR, stop taking the tablets and call your doctor right**  
1079 **away.** Do not take WELLBUTRIN SR again if you have a seizure.
- 1080 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
1081 severe, while taking WELLBUTRIN SR. The chance of high blood pressure may be  
1082 increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help  
1083 you stop smoking.
- 1084 • **Severe allergic reactions: Stop taking WELLBUTRIN SR and call your doctor right**  
1085 **away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the  
1086 mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble  
1087 breathing. These could be signs of a serious allergic reaction.
- 1088 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1089 taking WELLBUTRIN SR, including delusions (believe you are someone else),

1090 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are  
1091 against you), or feeling confused. If this happens to you, call your doctor.

1092

1093 The most common side effects of WELLBUTRIN SR are loss of appetite, dry mouth, skin rash,  
1094 sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble  
1095 sleeping, muscle pain, nausea, fast heart beat, sore throat, and urinating more often.

1096

1097 If you have nausea, you may want to take your medicine with food. If you have trouble sleeping,  
1098 do not take your medicine too close to bedtime.

1099

1100 Tell your doctor right away about any side effects that bother you.

1101

1102 These are not all the side effects of WELLBUTRIN SR. For a complete list, ask your doctor or  
1103 pharmacist.

1104

#### 1105 **How should I store WELLBUTRIN SR?**

1106 • Store WELLBUTRIN SR at room temperature. Store out of direct sunlight. Keep  
1107 WELLBUTRIN SR in its tightly closed bottle.

1108 • WELLBUTRIN SR tablets may have an odor.

1109

#### 1110 **General Information about WELLBUTRIN SR.**

1111 • Medicines are sometimes prescribed for conditions that are not mentioned in patient  
1112 information leaflets. Do not use WELLBUTRIN SR for a condition for which it was not  
1113 prescribed. Do not give WELLBUTRIN SR to other people, even if they have the same  
1114 symptoms you have. It may harm them. Keep WELLBUTRIN SR out of the reach of  
1115 children.

1116

1117 This leaflet summarizes important information about WELLBUTRIN SR. For more information,  
1118 talk with your doctor. You can ask your doctor or pharmacist for information about  
1119 WELLBUTRIN SR that is written for health professionals.

1120

#### 1121 **What are the ingredients in WELLBUTRIN SR?**

1122 Active ingredient: bupropion hydrochloride.

1123

1124 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1125 microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In  
1126 addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C  
1127 Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40  
1128 Lake. The tablets are printed with edible black ink.

1129

1130 \*The following are registered trademarks of their respective manufacturers: Nardil<sup>®</sup>/Warner  
1131 Lambert Company; Marplan<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

1132

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