

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

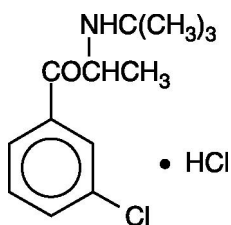
**Suicidality in Children and Adolescents**

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 or the  
46 re-uptake of serotonin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

### 163 **INDICATIONS AND USAGE**

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

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

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

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

### 184 **CONTRAINDICATIONS**

185 WELLBUTRIN is contraindicated in patients with a seizure disorder.

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

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

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

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

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

## 201 **WARNINGS**

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

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

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

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

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

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

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

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

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

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

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

275  
276 **Seizures:** Bupropion is associated with seizures in approximately 0.4% (4/1,000) of  
277 patients treated at doses up to 450 mg/day. This incidence of seizures may exceed that of  
278 other marketed antidepressants by as much as 4-fold. This relative risk is only an  
279 approximate estimate because no direct comparative studies have been conducted. The  
280 estimated seizure incidence for WELLBUTRIN increases almost tenfold between 450 and  
281 600 mg/day, which is twice the usually required daily dose (300 mg) and one and one-third  
282 the maximum recommended daily dose (450 mg). Given the wide variability among  
283 individuals and their capacity to metabolize and eliminate drugs this disproportionate  
284 increase in seizure incidence with dose incrementation calls for caution in dosing.

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

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

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

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

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



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

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

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

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

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

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

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

## 335 **PRECAUTIONS**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

544 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
545 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
546 there were no apparent adverse effects on offspring development.

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

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

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

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

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

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

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

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

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

588  
589 **ADVERSE REACTIONS** (see also WARNINGS and PRECAUTIONS)

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

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

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

611 Finally, it is important to emphasize that the tabulation does not reflect the relative severity  
 612 and/or clinical importance of the events. A better perspective on the serious adverse events  
 613 associated with the use of WELLBUTRIN is provided in WARNINGS and PRECAUTIONS.  
 614

615 **Table 1. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled**  
 616 **Clinical Trials\* (Percent of Patients Reporting)**

Adverse Experience	WELLBUTRIN Patients (n = 323)	Placebo Patients (n = 185)
Cardiovascular		
Cardiac arrhythmias	5.3	4.3
Dizziness	22.3	16.2
Hypertension	4.3	1.6
Hypotension	2.5	2.2
Palpitations	3.7	2.2
Syncope	1.2	0.5
Tachycardia	10.8	8.6
Dermatologic		
Pruritus	2.2	0.0
Rash	8.0	6.5



Gastrointestinal		
Anorexia	18.3	18.4
Appetite increase	3.7	2.2
Constipation	26.0	17.3
Diarrhea	6.8	8.6
Dyspepsia	3.1	2.2
Nausea/vomiting	22.9	18.9
Weight gain	13.6	22.7
Weight loss	23.2	23.2
Genitourinary		
Impotence	3.4	3.1
Menstrual complaints	4.7	1.1
Urinary frequency	2.5	2.2
Urinary retention	1.9	2.2
Musculoskeletal		
Arthritis	3.1	2.7
Neurological		
Akathisia	1.5	1.1
Akinesia/bradykinesia	8.0	8.6
Cutaneous temperature disturbance	1.9	1.6
Dry mouth	27.6	18.4
Excessive sweating	22.3	14.6
Headache/migraine	25.7	22.2
Impaired sleep quality	4.0	1.6
Increased salivary flow	3.4	3.8
Insomnia	18.6	15.7
Muscle spasms	1.9	3.2
Pseudoparkinsonism	1.5	1.6
Sedation	19.8	19.5
Sensory disturbance	4.0	3.2
Tremor	21.1	7.6
Neuropsychiatric		
Agitation	31.9	22.2
Anxiety	3.1	1.1
Confusion	8.4	4.9
Decreased libido	3.1	1.6
Delusions	1.2	1.1
Disturbed concentration	3.1	3.8
Euphoria	1.2	0.5
Hostility	5.6	3.8
Nonspecific		
Fatigue	5.0	8.6

Fever/chills	1.2	0.5
Respiratory Upper respiratory complaints	5.0	11.4
Special Senses Auditory disturbance	5.3	3.2
Blurred vision	14.6	10.3
Gustatory disturbance	3.1	1.1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 680 DRUG ABUSE AND DEPENDENCE

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

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

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

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

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

## 700 **OVERDOSAGE**

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

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

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

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

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

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

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

## 728 **DOSAGE AND ADMINISTRATION**

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

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

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

744

745 **Table 2. Dosing Regimen**

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

746

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

756 **Maintenance Treatment:** The lowest dose that maintains remission is recommended.

757 Although it is not known how long the patient should remain on WELLBUTRIN, it is generally  
758 recognized that acute episodes of depression require several months or longer of antidepressant  
759 drug treatment.

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

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

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

## 769 HOW SUPPLIED

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

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

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

775

## 776 MEDICATION GUIDE

### 777 WELLBUTRIN® (WELL byu-trin)

### 778 (bupropion hydrochloride) Tablets

779

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

784

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

789

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

791

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

794

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

797

1. There is a risk of suicidal thoughts or actions

798

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

799

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

800

4. There are benefits and risks when using antidepressants

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

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

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

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

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

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

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

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

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

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

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

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

842

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

844

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

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

859

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

862

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

864

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

870

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

872

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

875

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

879



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

882

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

884

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

889

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

892

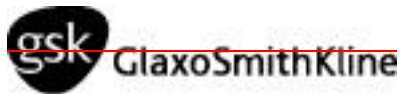
893 ~~This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
894 antidepressants.~~

895

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

897

898



899

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

905

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908 ~~May 2006~~ \_\_\_\_\_ ~~RL-2281~~

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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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915

**Patient Information**  
**WELLBUTRIN<sup>®</sup> (WELL-byu-trin)**  
**(bupropion hydrochloride) Tablets**

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

921  
922 **What is the most important information I should know about WELLBUTRIN?**

923  
924 **There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN, especially in**  
925 **people:**

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

928  
929 The chance of having seizures increases with higher doses of WELLBUTRIN. For more  
930 information, see the sections “Who should not take WELLBUTRIN?” and “What should I tell  
931 my doctor before using WELLBUTRIN?” Tell your doctor about all of your medical conditions  
932 and all the medicines you take. **Do not take any other medicines while you are using**  
933 **WELLBUTRIN unless your doctor has said it is okay to take them.**

934  
935 **If you have a seizure while taking WELLBUTRIN, stop taking the tablets and call your**  
936 **doctor right away.** Do not take WELLBUTRIN again if you have a seizure.

937  
938 **What is important information I should know and share with my family about taking**  
939 **antidepressants?**

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

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

949  
950 **What is WELLBUTRIN?**

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

953  
954 **Who should not take WELLBUTRIN?**

955 **Do not take WELLBUTRIN if you**

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

- 959 **Tablets or WELLBUTRIN XL Extended-Release Tablets.** Bupropion is the same  
960 ingredient that is in WELLBUTRIN.
- 961 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
962 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
  - 963 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
964 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
965 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
  - 966 • have or had an eating disorder such as anorexia nervosa or bulimia.
  - 967 • are allergic to the active ingredient in WELLBUTRIN, bupropion, or to any of the inactive  
968 ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN.
- 969

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

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

991  
992 ~~WELLBUTRIN has not been studied in children under the age of 18 years.~~

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

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

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

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

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

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

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

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

1038

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

1041

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

1043

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

1046

#### 1047 **How should I store WELLBUTRIN?**

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

1050

#### 1051 **General Information about WELLBUTRIN.**

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

1057

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

1061

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

1063 Active ingredient: bupropion hydrochloride.

1064

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

1070

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

1075

1076 **R<sub>x</sub> only**

1077

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

1079

1080 September 2006

MG-WT:2

1081



1082

1083

Manufactured by DSM Pharmaceuticals, Inc.

1084

Greenville, NC 27834 for

1085

GlaxoSmithKline

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Research Triangle Park, NC 27709

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~~May 2006~~September 2006

RL-~~2281~~2293

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

**Suicidality in Children and Adolescents**

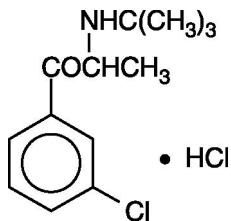
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of WELLBUTRIN SR or any other antidepressant in a child or adolescent must 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 or the re-  
45 uptake of serotonin. While the mechanism of action of bupropion, as with other antidepressants,  
46 is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic  
47 mechanisms.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 160 **CLINICAL TRIALS**

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

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

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

192 **INDICATIONS AND USAGE**

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

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

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

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

211 **CONTRAINDICATIONS**

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

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

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

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

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

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

228 **WARNINGS**

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

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

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

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

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

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

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

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

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

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

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

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

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

302  
303 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures  
304 is also related to patient factors, clinical situations, and concomitant medications, which  
305 must be considered in selection of patients for therapy with WELLBUTRIN SR.

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

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

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

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

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

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

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

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

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

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

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

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

## 366 PRECAUTIONS

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

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

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

371  
 372 In clinical studies, these symptoms were sometimes of sufficient magnitude to require  
 373 treatment with sedative/hypnotic drugs.

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

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



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

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

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

387

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

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

389

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

585 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
586 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
587 there were no apparent adverse effects on offspring development.

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

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

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

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

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

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

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

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

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

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

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

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

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

644

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

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

646

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

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

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

665  
 666

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

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



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

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

672 † Incidence based on the number of female patients.

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

674

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 747 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

## 770 **OVERDOSAGE**

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

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

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

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

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

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

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

## 798 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

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

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

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

#### 840 **HOW SUPPLIED**

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

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

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

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

852

853

### **MEDICATION GUIDE**

854

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

855

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

856

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

861  
862 **IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What**  
863 **is the most important information I should know about WELLBUTRIN SR?” It contains**  
864 **important information about this medication. It immediately follows the next section called**  
865 **“About Using Antidepressants in Children and Teenagers.”**

## 866 867 **About Using Antidepressants in Children and Teenagers**

868  
869 **What is the most important information I should know if my child is being prescribed an**  
870 **antidepressant?**

871  
872 Parents or guardians need to think about 4 important things when their child is prescribed an  
873 antidepressant:

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

### 878 879 **1. There is a Risk of Suicidal Thoughts or Actions**

880  
881 Children and teenager sometimes think about suicide, and many report trying to kill themselves.

882  
883 Antidepressants increase suicidal thoughts and actions in some children and teenagers. But  
884 suicidal thoughts and actions can also be caused by depression, a serious medical condition that  
885 is commonly treated with antidepressants. Thinking about killing yourself or trying to kill  
886 yourself is called *suicidality* or *being suicidal*.

887  
888 A large study combined the results of 24 different studies of children and teenagers with  
889 depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an  
890 antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients  
891 became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4  
892 out of every 100 patients became suicidal.

893  
894 **For some children and teenagers, the risks of suicidal actions may be especially high.** These  
895 include patients with

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

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

901

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

903

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

909

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

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

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

917

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

919

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

921

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

- 924 • Thoughts about suicide or dying
- 925 • Attempts to commit suicide
- 926 • New or worse depression
- 927 • New or worse anxiety
- 928 • Feeling very agitated or restless
- 929 • Panic attacks
- 930 • Difficulty sleeping (insomnia)
- 931 • New or worse irritability
- 932 • Acting aggressive, being angry, or violent
- 933 • Acting on dangerous impulses
- 934 • An extreme increase in activity and talking
- 935 • Other unusual changes in behavior or mood

936

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

939

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



941  
942 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses  
943 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases  
944 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also  
945 the risks of not treating it. You and your child should discuss all treatment choices with your  
946 healthcare provider, not just the use of antidepressants.

947  
948 Other side effects can occur with antidepressants (see section below).

949  
950 Of all antidepressants, only fluoxetine (~~Prozac~~PROZAC<sup>®</sup>)\* has been FDA approved to treat  
951 pediatric depression.

952  
953 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine  
954 (~~Prozac~~PROZAC<sup>®</sup>)\*, sertraline (~~Zoloft~~ZOLOFT<sup>®</sup>)\*, fluvoxamine (LUVOX<sup>®</sup>)\*, and  
955 clomipramine (~~Anafranil~~ANAFRANIL<sup>®</sup>)\*.

956  
957 Your healthcare provider may suggest other antidepressants based on the past experience of your  
958 child or other family members.

959  
960 **Is this all I need to know if my child is being prescribed an antidepressant?**

961  
962 No. This is a warning about the risk of suicidality. Other side effects can occur with  
963 antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the  
964 particular drug he or she is prescribing. Also ask about drugs to avoid when taking an  
965 antidepressant. Ask your healthcare provider or pharmacist where to find more information.

966  
967 ~~\*The following are registered trademarks of their respective manufacturers: Prozac<sup>®</sup>/Eli Lilly  
968 and Company; Zoloft<sup>®</sup>/Pfizer Pharmaceuticals; Anafranil<sup>®</sup>/Mallinckrodt Inc.~~

969  
970 ~~This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
971 antidepressants.~~

972  
973 ~~January 2005~~ ~~MG-MS:1~~

974  
975 

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989

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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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990  
-----  
991 **Patient Information**  
992 **WELLBUTRIN SR<sup>®</sup> (WELL-byu-trin)**  
993 **(bupropion hydrochloride) Sustained-Release Tablets**  
994  
995 ~~Read the Patient Information that comes with WELLBUTRIN SR before you start taking~~  
996 ~~WELLBUTRIN SR and each time you get a refill. There may be new information. This leaflet~~  
997 ~~does not take the place of talking with your doctor about your medical condition or your~~  
998 ~~treatment.~~  
999

1000 **What is the most important information I should know about WELLBUTRIN SR?**

1001  
1002 **There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN SR, especially**  
1003 **in people:**

- 1004 • with certain medical problems.  
1005 • who take certain medicines.

1006  
1007 The chance of having seizures increases with higher doses of WELLBUTRIN SR. For more  
1008 information, see the sections “Who should not take WELLBUTRIN SR?” and “What should I  
1009 tell my doctor before using WELLBUTRIN SR?” Tell your doctor about all of your medical  
1010 conditions and all the medicines you take. **Do not take any other medicines while you are**  
1011 **using WELLBUTRIN SR unless your doctor has said it is okay to take them.**

1012  
1013 **If you have a seizure while taking WELLBUTRIN SR, stop taking the tablets and call your**  
1014 **doctor right away.** Do not take WELLBUTRIN SR again if you have a seizure.  
1015

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

1018 Patients and their families should watch out for worsening depression or thoughts of suicide.  
1019 Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated,  
1020 panicky, irritable, hostile, aggressive, impulsive, severely restless, overly excited and  
1021 hyperactive, not being able to sleep, or other unusual changes in behavior. If this happens,  
1022 especially at the beginning of antidepressant treatment or after a change in dose, call your doctor.  
1023 ~~A patient Medication Guide will be provided to you with each prescription of~~  
1024 ~~WELLBUTRIN SR~~ For additional information, see section above entitled "About Using  
1025 Antidepressants in Children and Teenagers." WELLBUTRIN SR has not been studied in  
1026 children under the age of 18 and is not approved for use in children and teenagers.

1027  
1028 **What is WELLBUTRIN SR?**

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

1031

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

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

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

1048

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

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

- 1056 • **have liver problems**, especially cirrhosis of the liver.
- 1057 • have kidney problems.
- 1058 • have an eating disorder such as anorexia nervosa or bulimia.
- 1059 • have had a head injury.
- 1060 • have had a seizure (convulsion, fit).
- 1061 • have a tumor in your nervous system (brain or spine).
- 1062 • have had a heart attack, heart problems, or high blood pressure.
- 1063 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1064 • drink a lot of alcohol.
- 1065 • abuse prescription medicines or street drugs.
- 1066
- 1067 • **Tell your doctor about all the medicines you take**, including prescription and non-
- 1068 prescription medicines, vitamins, and herbal supplements. Many medicines increase your
- 1069 chances of having seizures or other serious side effects if you take them while you are using
- 1070 WELLBUTRIN SR.
- 1071

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

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

- 1075 • Take WELLBUTRIN SR exactly as prescribed by your doctor.
- 1076 • **Do not chew, cut, or crush WELLBUTRIN SR Tablets.** You must swallow the tablets
- 1077 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 1078 • Take WELLBUTRIN SR at the same time each day.
- 1079 • Take your doses of WELLBUTRIN SR at least 8 hours apart.
- 1080 • You may take WELLBUTRIN SR with or without food.
- 1081 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
- 1082 take your next tablet at the regular time. **This is very important.** Too much
- 1083 WELLBUTRIN SR can increase your chance of having a seizure.
- 1084 • If you take too much WELLBUTRIN SR, or overdose, call your local emergency room or
- 1085 poison control center right away.
- 1086 • **Do not take any other medicines while using WELLBUTRIN SR unless your doctor has**
- 1087 **told you it is okay.**
- 1088 • It may take several weeks for you to feel that WELLBUTRIN SR is working. Once you feel
- 1089 better, it is important to keep taking WELLBUTRIN SR exactly as directed by your doctor.
- 1090 Call your doctor if you do not feel WELLBUTRIN SR is working for you.
- 1091 • Do not change your dose or stop taking WELLBUTRIN SR without talking with your doctor
- 1092 first.
- 1093

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

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

1100

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

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

1117

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

1121

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

1124

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

1126

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

1129

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

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

1134

1135 **General Information about WELLBUTRIN SR.**

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

1141  
1142 This ~~leaflet~~Medication Guide summarizes important information about WELLBUTRIN SR. For  
1143 more information, talk with your doctor. You can ask your doctor or pharmacist for information  
1144 about WELLBUTRIN SR that is written for health professionals.

1145  
1146 **What are the ingredients in WELLBUTRIN SR?**

1147 Active ingredient: bupropion hydrochloride.

1148  
1149 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1150 microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. In  
1151 addition, the 100-mg tablet contains FD&C Blue No. 1 Lake, the 150-mg tablet contains FD&C  
1152 Blue No. 2 Lake and FD&C Red No. 40 Lake, and the 200-mg tablet contains FD&C Red No. 40  
1153 Lake. The tablets are printed with edible black ink.

1154  
1155 \*The following are registered trademarks of their respective manufacturers: PROZAC®/Eli Lilly  
1156 and Company; ZOLOFT®/Pfizer Pharmaceuticals; LUVOX®/Solvay Pharmaceuticals, Inc;  
1157 ANAFRANIL®/Mallinckrodt Inc; NardilNARDIL®/Warner Lambert Company;  
1158 MarplanMARPLAN®/Oxford Pharmaceutical Services, Inc.

1159  
1160 **R<sub>x</sub> only**

1161  
1162 **This Medication Guide has been approved by the U.S. Food and Drug Administration.**

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1164 September 2006 MG-MS:2



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