

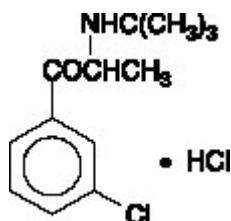
**WELLBUTRIN XL<sup>®</sup>**  
**(bupropion hydrochloride extended-release tablets)**

**Suicidality and Antidepressant Drugs**

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

**DESCRIPTION**

WELLBUTRIN XL (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:



WELLBUTRIN XL Tablets are supplied for oral administration as 150-mg and 300-mg, creamy-white to pale yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: ethylcellulose aqueous dispersion (NF), glyceryl behenate, methacrylic acid copolymer dispersion (NF), polyvinyl alcohol, polyethylene

36 glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black  
37 ink.

38 The insoluble shell of the extended-release tablet may remain intact during gastrointestinal  
39 transit and is eliminated in the feces.

## 40 **CLINICAL PHARMACOLOGY**

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

46 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and  
47 pharmacokinetics of the individual enantiomers have not been studied. The mean elimination  
48 half-life ( $\pm$ SD) of bupropion after chronic dosing is 21 ( $\pm$ 9) hours, and steady-state plasma  
49 concentrations of bupropion are reached within 8 days.

50 In a study comparing 14-day dosing with WELLBUTRIN XL Tablets 300 mg once daily to  
51 the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was  
52 demonstrated for peak plasma concentration and area under the curve for bupropion and the  
53 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion).  
54 Additionally, in a study comparing 14-day dosing with WELLBUTRIN XL Tablets 300 mg once  
55 daily to the sustained-release formulation of bupropion at 150 mg 2 times daily, equivalence was  
56 demonstrated for peak plasma concentration and area under the curve for bupropion and the  
57 3 metabolites.

58 **Absorption:** Following oral administration of WELLBUTRIN XL Tablets to healthy  
59 volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours and  
60 food did not affect the  $C_{max}$  or AUC of bupropion.

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

65 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
66 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
67 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
68 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
69 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
70 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
71 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of  
72 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency  
73 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,  
74 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is

75 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are  
76 5-fold less potent than bupropion. This may be of clinical importance because the plasma  
77 concentrations of the metabolites are as high or higher than those of bupropion.

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

83 In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours  
84 after administration of WELLBUTRIN XL. Following administration of WELLBUTRIN XL,  
85 peak plasma concentrations of hydroxybupropion are approximately 7 times the peak level of the  
86 parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20  
87 ( $\pm 5$ ) hours, and its AUC at steady state is about 13 times that of bupropion. The times to peak  
88 concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar  
89 to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer,  
90 approximately 33 ( $\pm 10$ ) and 37 ( $\pm 13$ ) hours, respectively, and steady-state AUCs are 1.4 and  
91 7 times that of bupropion, respectively.

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

94 **Elimination:** Following oral administration of 200 mg of  $^{14}\text{C}$ -bupropion in humans, 87% and  
95 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the  
96 fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent  
97 with the extensive metabolism of bupropion.

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

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

112 The second study showed no statistically significant differences in the pharmacokinetics of  
113 bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis  
114 compared to 8 healthy volunteers. However, more variability was observed in some of the

115 pharmacokinetic parameters for bupropion (AUC, C<sub>max</sub>, and T<sub>max</sub>) and its active metabolites (t<sub>1/2</sub>)  
116 in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic  
117 cirrhosis, the bupropion C<sub>max</sub> and AUC were substantially increased (mean difference: by  
118 approximately 70% and 3-fold, respectively) and more variable when compared to values in  
119 healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with  
120 severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion,  
121 the mean C<sub>max</sub> was approximately 69% lower. For the combined amino-alcohol isomers  
122 threohydrobupropion and erythrohydrobupropion, the mean C<sub>max</sub> was approximately 31% lower.  
123 The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for  
124 threo/erythrohydrobupropion. The median T<sub>max</sub> was observed 19 hours later for  
125 hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for  
126 hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively,  
127 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,  
128 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

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

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

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

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

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

## 157 **CLINICAL TRIALS**

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

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

183 Although there are no independent trials demonstrating the antidepressant effectiveness of  
184 WELLBUTRIN XL, studies have demonstrated similar bioavailability of WELLBUTRIN XL to  
185 both the immediate-release formulation and to the sustained-release formulation of bupropion  
186 under steady-state conditions, i.e., WELLBUTRIN XL 300 mg once daily was shown to have  
187 bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release  
188 formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release  
189 formulation of bupropion, with regard to both peak plasma concentration and extent of  
190 absorption, for parent drug and metabolites.

191 **Seasonal Affective Disorder:** The efficacy of WELLBUTRIN XL for the prevention of  
192 seasonal major depressive episodes associated with seasonal affective disorder was established in  
193 3 double-blind, placebo-controlled trials in adult outpatients with a history of major depressive

194 disorder with an autumn-winter seasonal pattern (as defined by DSM-IV criteria). Treatment was  
195 initiated prior to the onset of symptoms in the autumn (September to November) and was  
196 discontinued following a 2 week taper that began the first week of spring (fourth week of  
197 March), resulting in a treatment duration of approximately 4 to 6 months for the majority of  
198 patients. At the start of the study, patients were randomized to receive placebo or  
199 WELLBUTRIN XL 150 mg once daily for 1 week, followed by up-titration to 300 mg once  
200 daily. Patients who were deemed by the investigator to be unlikely or unable to tolerate 300 mg  
201 once daily were allowed to remain on, or had their dose reduced to, 150 mg once daily. The  
202 mean WELLBUTRIN XL doses in the 3 studies ranged from 257 to 280 mg/day.

203 In these 3 trials, the percentage of patients who were depression-free at the end of treatment  
204 was significantly higher for WELLBUTRIN XL than for placebo: 81.4% vs 69.7%, 87.2% vs  
205 78.7%, and 84.0% vs 69.0% for Study 1, 2 and 3, respectively; with a depression-free rate for the  
206 3 studies combined of 84.3% vs 72.0%.

## 207 **INDICATIONS AND USAGE**

208 **Major Depressive Disorder:** WELLBUTRIN XL is indicated for the treatment of major  
209 depressive disorder.

210 The efficacy of bupropion in the treatment of a major depressive episode was established in  
211 two 4-week controlled trials of inpatients and in one 6-week controlled trial of outpatients whose  
212 diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic  
213 and Statistical Manual (DSM) (see CLINICAL TRIALS).

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

221 The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks  
222 following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the  
223 sustained-release formulation of bupropion (see CLINICAL TRIALS). Nevertheless, the  
224 physician who elects to use WELLBUTRIN XL for extended periods should periodically  
225 reevaluate the long-term usefulness of the drug for the individual patient.

226 **Seasonal Affective Disorder:** WELLBUTRIN XL is indicated for the prevention of seasonal  
227 major depressive episodes in patients with a diagnosis of seasonal affective disorder.

228 The efficacy of WELLBUTRIN XL for the prevention of seasonal major depressive episodes  
229 was established in 3 controlled trials of adult outpatients with a history of major depressive  
230 disorder with an autumn-winter seasonal pattern as defined by Diagnostic and Statistical Manual  
231 of Mental Disorders, 4th edition (DSM-IV) criteria (see CLINICAL TRIALS).

232 Seasonal affective disorder is characterized by recurrent major depressive episodes, most  
233 commonly occurring during the autumn and/or winter months. Episodes may last up to 6 months  
234 in duration, typically beginning in the autumn and remitting in the springtime. Although patients  
235 with seasonal affective disorder may have depressive episodes during other times of the year, the  
236 diagnosis of seasonal affective disorder requires that the number of seasonal episodes  
237 substantially outnumber the number of non-seasonal episodes during the individual's lifetime.

## 238 **CONTRAINDICATIONS**

239 WELLBUTRIN XL is contraindicated in patients with a seizure disorder.

240 WELLBUTRIN XL is contraindicated in patients treated with ZYBAN<sup>®</sup> (bupropion  
241 hydrochloride) Sustained-Release Tablets; WELLBUTRIN<sup>®</sup> (bupropion hydrochloride), the  
242 immediate-release formulation; WELLBUTRIN SR<sup>®</sup> (bupropion hydrochloride), the sustained-  
243 release formulation; or any other medications that contain bupropion because the incidence of  
244 seizure is dose dependent.

245 WELLBUTRIN XL is contraindicated in patients with a current or prior diagnosis of bulimia  
246 or anorexia nervosa because of a higher incidence of seizures noted in patients treated for  
247 bulimia with the immediate-release formulation of bupropion.

248 WELLBUTRIN XL is contraindicated in patients undergoing abrupt discontinuation of  
249 alcohol or sedatives (including benzodiazepines).

250 The concurrent administration of WELLBUTRIN XL Tablets and a monoamine oxidase  
251 (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an  
252 MAO inhibitor and initiation of treatment with WELLBUTRIN XL Tablets.

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

## 255 **WARNINGS**

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

270 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
 271 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24  
 272 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of  
 273 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of  
 274 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000  
 275 patients. There was considerable variation in risk of suicidality among drugs, but a tendency  
 276 toward an increase in the younger patients for almost all drugs studied. There were differences in  
 277 absolute risk of suicidality across the different indications, with the highest incidence in MDD.  
 278 The risk differences (drug vs placebo), however, were relatively stable within age strata and  
 279 across indications. These risk differences (drug-placebo difference in the number of cases of  
 280 suicidality per 1,000 patients treated) are provided in Table 1.

281  
 282

**Table 1**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

283

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

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

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

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

300 Consideration should be given to changing the therapeutic regimen, including possibly  
 301 discontinuing the medication, in patients whose depression is persistently worse, or who are



302 experiencing emergent suicidality or symptoms that might be precursors to worsening depression  
303 or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the  
304 patient's presenting symptoms.

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

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

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

323 **Patients should be made aware that WELLBUTRIN XL contains the same active**  
324 **ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that**  
325 **WELLBUTRIN XL should not be used in combination with ZYBAN, or any other**  
326 **medications that contain bupropion, such as WELLBUTRIN SR (bupropion**  
327 **hydrochloride), the sustained-release formulation or WELLBUTRIN (bupropion**  
328 **hydrochloride), the immediate-release formulation.**

329  
330 **Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures  
331 is also related to patient factors, clinical situations, and concomitant medications, which  
332 must be considered in selection of patients for therapy with WELLBUTRIN XL.

333 **WELLBUTRIN XL should be discontinued and not restarted in patients who experience a**  
334 **seizure while on treatment.**

335 **As WELLBUTRIN XL is bioequivalent to both the immediate-release formulation of**  
336 **bupropion and to the sustained-release formulation of bupropion, the seizure incidence**  
337 **with WELLBUTRIN XL, while not formally evaluated in clinical trials, may be similar to**  
338 **that presented below for the immediate-release and sustained-release formulations of**  
339 **bupropion.**

- 340 • **Dose:** At doses up to 300 mg/day of the sustained-release formulation of bupropion  
341 (WELLBUTRIN SR), the incidence of seizure is approximately 0.1% (1/1,000).

342 Data for the immediate-release formulation of bupropion revealed a seizure  
343 incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in  
344 patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%)  
345 may exceed that of some other marketed antidepressants.

346 Additional data accumulated for the immediate-release formulation of bupropion  
347 suggested that the estimated seizure incidence increases almost tenfold between 450 and  
348 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the  
349 maximum recommended daily dose (450 mg) of WELLBUTRIN XL Tablets. This  
350 disproportionate increase in seizure incidence with dose incrementation calls for  
351 caution in dosing.

- 352 • **Patient factors:** Predisposing factors that may increase the risk of seizure with  
353 bupropion use include history of head trauma or prior seizure, central nervous system  
354 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications  
355 that lower seizure threshold.
- 356 • **Clinical situations:** Circumstances associated with an increased seizure risk include,  
357 among others, excessive use of alcohol or sedatives (including benzodiazepines);  
358 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and  
359 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 360 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,  
361 theophylline, systemic steroids) are known to lower seizure threshold.

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

- 365 • the total daily dose of WELLBUTRIN XL Tablets does *not* exceed 450 mg,
- 366 • the rate of incrementation of dose is gradual.

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

371 **Hepatic Impairment:** WELLBUTRIN XL should be used with extreme caution in patients  
372 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,  
373 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is  
374 likely to occur in such patients to a greater extent than usual. The dose should not exceed  
375 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY,  
376 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

381 **PRECAUTIONS**

382 **General: Agitation and Insomnia:** Increased restlessness, agitation, anxiety, and insomnia,  
 383 especially shortly after initiation of treatment, have been associated with treatment with  
 384 bupropion. In 3 placebo-controlled clinical trials of seasonal affective disorder with  
 385 WELLBUTRIN XL, the incidence of agitation, anxiety, and insomnia are shown in Table 2.  
 386

387 **Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of**  
 388 **WELLBUTRIN XL for Seasonal Affective Disorder**

Adverse Event Term	WELLBUTRIN XL 150 to 300 mg/day (n = 537)	Placebo (n = 511)
Agitation	2%	<1%
Anxiety	7%	5%
Insomnia	20%	13%

389  
 390 Patients in placebo-controlled trials of major depressive disorder with WELLBUTRIN SR, the  
 391 sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as  
 392 shown in Table 3.  
 393

394 **Table 3. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of**  
 395 **WELLBUTRIN SR for Major Depressive Disorder**

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%

396  
 397 In clinical studies of major depressive disorder, these symptoms were sometimes of sufficient  
 398 magnitude to require treatment with sedative/hypnotic drugs.

399 Symptoms in these studies were sufficiently severe to require discontinuation of treatment in  
 400 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion  
 401 sustained-release tablets and 0.8% of patients treated with placebo.

402 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** Depressed  
 403 patients treated with bupropion have been reported to show a variety of neuropsychiatric signs  
 404 and symptoms, including delusions, hallucinations, psychosis, concentration disturbance,  
 405 paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or  
 406 withdrawal of treatment.

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

410 **Altered Appetite and Weight:** In 3 placebo-controlled clinical trials of seasonal affective  
411 disorder with WELLBUTRIN XL, the percentage of patients with weight gain or weight loss are  
412 shown in Table 4.

413

414 **Table 4. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of**  
415 **WELLBUTRIN XL for Seasonal Affective Disorder**

Weight Change	WELLBUTRIN XL 150 to 300 mg/day (n = 537)	Placebo (n = 511)
Gained >5 lbs	11%	21%
Lost >5 lbs	23%	11%

416

417 In placebo-controlled studies of major depressive disorder using WELLBUTRIN SR, the  
418 sustained-release formulation of bupropion, patients experienced weight gain or weight loss as  
419 shown in Table 5.

420

421 **Table 5. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of**  
422 **WELLBUTRIN SR for Major Depressive Disorder**

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%

423

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

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

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

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

443 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN<sup>®</sup>  
444 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of  
445 sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a  
446 higher incidence of treatment-emergent hypertension in patients treated with the combination of  
447 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the  
448 combination of sustained-release bupropion and NTS had treatment-emergent hypertension  
449 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,  
450 and placebo, respectively. The majority of these patients had evidence of preexisting  
451 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and  
452 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension  
453 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure  
454 is recommended in patients who receive the combination of bupropion and nicotine replacement.

455 There is no clinical experience establishing the safety of WELLBUTRIN XL Tablets in  
456 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care  
457 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed  
458 patients who had previously developed orthostatic hypotension while receiving tricyclic  
459 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with  
460 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine  
461 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in  
462 2 patients for exacerbation of baseline hypertension.

463 **Hepatic Impairment:** WELLBUTRIN XL should be used with extreme caution in patients  
464 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.  
465 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including  
466 mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in  
467 patients with mild to moderate hepatic cirrhosis.

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

471 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
472 patients with renal impairment. An inter-study comparison between normal subjects and patients  
473 with end-stage renal failure demonstrated that the parent drug  $C_{max}$  and AUC values were  
474 comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
475 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage

476 renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are  
477 further metabolized and subsequently excreted by the kidneys. WELLBUTRIN XL should be  
478 used with caution in patients with renal impairment and a reduced frequency and/or dose should  
479 be considered as bupropion and the metabolites of bupropion may accumulate in such patients to  
480 a greater extent than usual. The patient should be closely monitored for possible adverse effects  
481 that could indicate high drug or metabolite levels.

482 **Information for Patients:** Prescribers or other health professionals should inform patients,  
483 their families, and their caregivers about the benefits and risks associated with treatment with  
484 WELLBUTRIN XL and should counsel them in its appropriate use. A patient Medication Guide  
485 about “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal  
486 Thoughts or Actions” and other important information about using WELLBUTRIN XL is  
487 available for WELLBUTRIN XL. The prescriber or health professional should instruct patients,  
488 their families, and their caregivers to read the Medication Guide and should assist them in  
489 understanding its contents. Patients should be given the opportunity to discuss the contents of the  
490 Medication Guide and to obtain answers to any questions they may have. The complete text of  
491 the Medication Guide is reprinted at the end of this document.

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

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

505 Patients should be made aware that WELLBUTRIN XL contains the same active ingredient  
506 found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN XL  
507 should not be used in combination with ZYBAN or any other medications that contain bupropion  
508 hydrochloride (such as WELLBUTRIN SR, the sustained-release formulation, and  
509 WELLBUTRIN, the immediate-release formulation).

510 Patients should be told that WELLBUTRIN XL should be discontinued and not restarted if  
511 they experience a seizure while on treatment.

512 Patients should be told that any CNS-active drug like WELLBUTRIN XL Tablets may impair  
513 their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently,  
514 until they are reasonably certain that WELLBUTRIN XL Tablets do not adversely affect their

515 performance, they should refrain from driving an automobile or operating complex, hazardous  
516 machinery.

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

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

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

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

528 Patients should be advised that they may notice in their stool something that looks like a  
529 tablet. This is normal. The medication in WELLBUTRIN XL is contained in a non-absorbable  
530 shell that has been specially designed to slowly release drug in the body. When this process is  
531 completed, the empty shell is eliminated from the body.

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

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

536 Because bupropion is extensively metabolized, the coadministration of other drugs may affect  
537 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to  
538 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
539 interaction between WELLBUTRIN XL and drugs that are substrates or inhibitors of the  
540 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro  
541 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
542 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
543 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
544 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant  
545 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites  
546 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg  
547 tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine,  
548 the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were  
549 16% and 32% increases in the AUC and  $C_{max}$ , respectively, of the combined moieties of  
550 threohydrobupropion and erythrohydrobupropion.

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

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

555 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
556 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to  
557 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.  
558 Nevertheless, there may be the potential for clinically important alterations of blood levels of  
559 coadministered drugs.

560 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most  
561 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are  
562 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this  
563 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a  
564 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6  
565 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of  
566 50 mg desipramine increased the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of  
567 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the  
568 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6  
569 has not been formally studied.

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

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

581 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
582 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
583 Administration of WELLBUTRIN XL Tablets to patients receiving either levodopa or  
584 amantadine concurrently should be undertaken with caution, using small initial doses and  
585 gradual dose increases.

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

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

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



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

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

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

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

617 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
618 7 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
619 there were no apparent adverse effects on offspring development.

620 One study has been conducted in pregnant women. This retrospective, managed-care database  
621 study assessed the risk of congenital malformations overall, and cardiovascular malformations  
622 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
623 malformations following exposure to other antidepressants in the first trimester and bupropion  
624 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
625 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
626 showed no greater risk for congenital malformations overall, or cardiovascular malformations  
627 specifically, following first trimester bupropion exposure compared to exposure to all other  
628 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of  
629 this study have not been corroborated. WELLBUTRIN XL should be used during pregnancy  
630 only if the potential benefit justifies the potential risk to the fetus.

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

634 **Labor and Delivery:** The effect of WELLBUTRIN XL Tablets on labor and delivery in  
635 humans is unknown.

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

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

644 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with  
645 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were  $\geq 65$   
646 years old and 47 were  $\geq 75$  years old. In addition, several hundred patients 65 and over  
647 participated in clinical trials using the immediate-release formulation of bupropion (depression  
648 studies). No overall differences in safety or effectiveness were observed between these subjects  
649 and younger subjects. Reported clinical experience has not identified differences in responses  
650 between the elderly and younger patients, but greater sensitivity of some older individuals cannot  
651 be ruled out.

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

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

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

662 **Major Depressive Disorder:** WELLBUTRIN XL has been demonstrated to have similar  
663 bioavailability both to the immediate-release formulation of bupropion and to the sustained-  
664 release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information  
665 included under this subsection is based primarily on data from controlled clinical trials with  
666 WELLBUTRIN SR Tablets, the sustained-release formulation of bupropion.

667 **Adverse Events Leading to Discontinuation of Treatment With WELLBUTRIN or**  
668 **WELLBUTRIN SR:** In placebo-controlled clinical trials, 9% and 11% of patients treated with  
669 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of  
670 patients treated with placebo discontinued treatment due to adverse events. The specific adverse  
671 events in these trials that led to discontinuation in at least 1% of patients treated with either

672 300 mg/day or 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of  
673 bupropion, and at a rate at least twice the placebo rate are listed in Table 6.

674  
675 **Table 6. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials**  
676 **for Major Depressive Disorder**

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

677  
678 In clinical trials with the immediate-release formulation of bupropion, 10% of patients and  
679 volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition  
680 to those listed above for the sustained-release formulation of bupropion, include vomiting,  
681 seizures, and sleep disturbances.

682 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**  
683 **Treated With WELLBUTRIN or WELLBUTRIN SR:** Table 7 enumerates  
684 treatment-emergent adverse events that occurred among patients treated with 300 and  
685 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled  
686 trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more  
687 and were more frequent than in the placebo group are included. Reported adverse events were  
688 classified using a COSTART-based Dictionary.

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

696 Finally, it is important to emphasize that the tabulation does not reflect the relative severity  
697 and/or clinical importance of the events. A better perspective on the serious adverse events  
698 associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS  
699 sections.

700

701 **Table 7. Treatment-Emergent Adverse Events in Placebo-Controlled Trials\*for**  
702 **Major Depressive Disorder**

Body System/ Adverse Event	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
<b>Body (General)</b>			
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%	—
<b>Cardiovascular</b>			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
<b>Digestive</b>			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
<b>Musculoskeletal</b>			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
<b>Nervous system</b>			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%

Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage <sup>†</sup>	0%	2%	—
Urinary tract infection	1%	0%	—

703 \* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day  
704 of the sustained-release formulation of bupropion, but equally or more frequently in the  
705 placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain,  
706 bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain,  
707 respiratory disorder, rhinitis, and tooth disorder.

708 † Incidence based on the number of female patients.

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

710

711 Additional events to those listed in Table 7 that occurred at an incidence of at least 1% in  
712 controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day)  
713 and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%),  
714 hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase  
715 (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%),

716 impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%),  
717 decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and  
718 gustatory disturbance (3% vs 1%).

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

720 Adverse events from Table 7 occurring in at least 5% of patients treated with the  
721 sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed  
722 below for the 300- and 400-mg/day dose groups.

723 ***300 mg/day of WELLBUTRIN SR:*** Anorexia, dry mouth, rash, sweating, tinnitus, and  
724 tremor.

725 ***400 mg/day of WELLBUTRIN SR:*** Abdominal pain, agitation, anxiety, dizziness, dry  
726 mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary  
727 frequency.

728 ***Seasonal Affective Disorder: Adverse Events Leading to Discontinuation of***

729 ***Treatment With WELLBUTRIN XL:*** In placebo-controlled clinical trials, 9% of patients  
730 treated with WELLBUTRIN XL and 5% of patients treated with placebo discontinued treatment  
731 due to adverse events. The adverse events in these trials that led to discontinuation in at least 1%  
732 of patients treated with WELLBUTRIN XL and at a rate numerically greater than the placebo  
733 rate are insomnia (2% vs <1%) and headache (1% vs <1%).

734 ***Adverse Events Occurring at an Incidence of 2% or More Among Patients***

735 ***Treated With Wellbutrin XL:*** Table 8 enumerates treatment-emergent adverse events that  
736 occurred among patients treated with WELLBUTRIN XL for up to approximately 6 months in  
737 3 placebo-controlled trials. Events that occurred at an incidence of 2% or more and were more  
738 frequent than in the placebo group are included. Reported adverse events were classified using a  
739 MedDRA-based Dictionary.

740 Accurate estimates of the incidence of adverse events associated with the use of any drug are  
741 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician  
742 judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward  
743 events in the course of usual medical practice where patient characteristics and other factors  
744 differ from those that prevailed in the clinical trials. These incidence figures also cannot be  
745 compared with those obtained from other clinical studies involving related drug products as each  
746 group of drug trials is conducted under a different set of conditions; e.g., different patient  
747 populations, different treatment durations.

748 Finally, it is important to emphasize that the tabulation does not reflect the relative severity  
749 and/or clinical importance of the events. A better perspective on the serious adverse events  
750 associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS  
751 sections.

752

753  
754

**Table 8. Treatment-Emergent Adverse Events\* in Placebo-Controlled Trials of Seasonal Affective Disorder**

System Organ Class/ Preferred Term	WELLBUTRIN XL (n = 537)	Placebo (n = 511)
Gastrointestinal Disorder		
Dry Mouth	26%	15%
Nausea	13%	8%
Constipation	9%	2%
Flatulence	6%	3%
Abdominal pain	2%	<1%
Nervous System Disorders		
Headache	34%	26%
Dizziness	6%	5%
Tremor	3%	<1%
Infections and Infestations		
Nasopharyngitis	13%	12%
Upper respiratory tract infection	9%	8%
Sinusitis	5%	4%
Psychiatric Disorders		
Insomnia	20%	13%
Anxiety	7%	5%
Abnormal dreams	3%	2%
Agitation	2%	<1%
Musculoskeletal and Connective Tissue Disorders		
Myalgia	3%	2%
Pain in extremity	3%	2%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	4%	3%
General Disorders and Administration Site Conditions		
Feeling jittery	3%	2%
Skin and Subcutaneous Tissue Disorders		
Rash	3%	2%
Metabolism and Nutrition Disorders		
Decreased appetite	4%	1%
Reproductive System and Breast Disorders		
Dysmenorrhea	2%	<1%

Ear and Labyrinth Disorders Tinnitus	3%	<1%
Vascular Disorders Hypertension	2%	0%

755 \* Adverse events that occurred in at least 2% of patients treated with WELLBUTRIN XL, but  
756 equally or more frequently in the placebo group, were: abdominal pain upper, arthralgia, back  
757 pain, diarrhea, dyspepsia, fatigue, gastroenteritis viral, hyperhidrosis, influenza, irritability,  
758 migraine, nasal congestion, neck pain, palpitations, pharyngolaryngeal pain, sinus congestion.

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

761 Adverse events from Table 8 that occurred in at least 5% of patients treated with  
762 WELLBUTRIN XL and at a rate at least twice the placebo rate were constipation and flatulence.

763 ***Adverse Events During Taper or Following Discontinuation of***

764 ***WELLBUTRIN XL:*** Adverse events with onset during the 2 weeks following down-titration of  
765 WELLBUTRIN XL from 300 mg/day to 150 mg/day were reported by 14% of patients  
766 compared to 18% of patients who continued on placebo.

767 Adverse events with onset during the 2 weeks following discontinuation of  
768 WELLBUTRIN XL were reported by 9% of patients compared with 12% of patients following  
769 discontinuation of placebo.

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

771 **Experience of Bupropion:** In addition to the adverse events noted above, the following  
772 events have been reported in clinical trials and postmarketing experience with the  
773 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,  
774 as well as in clinical trials and postmarketing clinical experience with the immediate-release  
775 formulation of bupropion.

776 Adverse events for which frequencies are provided below occurred in clinical trials with the  
777 sustained-release formulation of bupropion. The frequencies represent the proportion of patients  
778 who experienced a treatment-emergent adverse event on at least one occasion in  
779 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients  
780 who experienced an adverse event requiring discontinuation of treatment in an open-label  
781 surveillance study with the sustained-release formulation of bupropion (n = 3,100). All  
782 treatment-emergent adverse events are included except those listed in Tables 2 through 8, those  
783 events listed in other safety-related sections, those adverse events subsumed under COSTART  
784 terms that are either overly general or excessively specific so as to be uninformative, those  
785 events not reasonably associated with the use of the drug, and those events that were not serious  
786 and occurred in fewer than 2 patients. Events of major clinical importance are described in the  
787 WARNINGS and PRECAUTIONS sections of the labeling.

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



790 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
791 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

792 Adverse events for which frequencies are not provided occurred in clinical trials or  
793 postmarketing experience with bupropion. Only those adverse events not previously listed for  
794 sustained-release bupropion are included. The extent to which these events may be associated  
795 with WELLBUTRIN XL is unknown.

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

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

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

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

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

814 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed  
815 was glycosuria.

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

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

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

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

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

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

### 833 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

### 856 **OVERDOSAGE**

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

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

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

869 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
870 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
871 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
872 symptomatic patients.

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

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

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

## 884 **DOSAGE AND ADMINISTRATION**

885 **General Dosing Considerations:** It is particularly important to administer  
886 WELLBUTRIN XL Tablets in a manner most likely to minimize the risk of seizure (see  
887 WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness,  
888 and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary,  
889 these effects may be managed by temporary reduction of dose or the short-term administration of  
890 an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required  
891 beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses.  
892 If distressing, untoward effects supervene, dose escalation should be stopped.  
893 WELLBUTRIN XL should be swallowed whole and not crushed, divided, or chewed.  
894 WELLBUTRIN XL may be taken without regard to meals.

895 **Major Depressive Disorder: Initial Treatment:** The usual adult target dose for  
896 WELLBUTRIN XL Tablets is 300 mg/day, given once daily in the morning. Dosing with  
897 WELLBUTRIN XL Tablets should begin at 150 mg/day given as a single daily dose in the  
898 morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target  
899 dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval  
900 of at least 24 hours between successive doses.

901 **Increasing the Dosage Above 300 mg/day:** As with other antidepressants, the full  
902 antidepressant effect of WELLBUTRIN XL Tablets may not be evident until 4 weeks of  
903 treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single  
904 dose, may be considered for patients in whom no clinical improvement is noted after several  
905 weeks of treatment at 300 mg/day.

906 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require  
907 several months or longer of sustained pharmacological therapy beyond response to the acute

908 episode. It is unknown whether or not the dose of WELLBUTRIN XL needed for maintenance  
909 treatment is identical to the dose needed to achieve an initial response. Patients should be  
910 periodically reassessed to determine the need for maintenance treatment and the appropriate dose  
911 for such treatment.

912 **Seasonal Affective Disorder:** For the prevention of seasonal major depressive episodes  
913 associated with seasonal affective disorder, WELLBUTRIN XL should generally be initiated in  
914 the autumn prior to the onset of depressive symptoms. Treatment should continue through the  
915 winter season and should be tapered and discontinued in early spring. The timing of initiation  
916 and duration of treatment should be individualized based on the patient's historical pattern of  
917 seasonal major depressive episodes. Patients whose seasonal depressive episodes are infrequent  
918 or not associated with significant impairment should not generally be treated prophylactically.

919 Dosing with WELLBUTRIN XL Tablets should begin at 150 mg/day given as a single daily  
920 dose in the morning. If the 150-mg initial dose is adequately tolerated, the dose of  
921 WELLBUTRIN XL should be increased to the 300-mg/day dose after 1 week. If the 300-mg  
922 dose is not adequately tolerated, the dose can be reduced to 150 mg/day. The usual adult target  
923 dose for WELLBUTRIN XL Tablets is 300 mg/day, given once daily in the morning.

924 For patients taking 300 mg/day during the autumn-winter season, the dose should be tapered  
925 to 150 mg/day for 2 weeks prior to discontinuation.

926 Doses of WELLBUTRIN XL above 300 mg/day have not been studied for the prevention of  
927 seasonal major depressive episodes.

#### 928 **Switching Patients from WELLBUTRIN Tablets or from WELLBUTRIN SR**

929 **Sustained-Release Tablets:** When switching patients from WELLBUTRIN Tablets to  
930 WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to  
931 WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently  
932 being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day)  
933 may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being  
934 treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg  
935 twice daily) may be switched to WELLBUTRIN XL 300 mg once daily.

#### 936 **Dosage Adjustment for Patients With Impaired Hepatic Function:**

937 WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic  
938 cirrhosis. The dose should not exceed 150 mg every other day in these patients.

939 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including  
940 mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in  
941 patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY,  
942 WARNINGS, and PRECAUTIONS).

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

946 **HOW SUPPLIED**

947 WELLBUTRIN XL Extended-Release Tablets, 150 mg of bupropion hydrochloride, are  
948 creamy-white to pale yellow, round, tablets printed with “WELLBUTRIN XL 150” in bottles of  
949 30 (NDC 0173-0730-01) and 90 (NDC 0173-0730-02).

950 WELLBUTRIN XL Extended-Release Tablets, 300 mg of bupropion hydrochloride, are  
951 creamy-white to pale yellow, round, tablets printed with “WELLBUTRIN XL 300” in bottles of  
952 30 (NDC 0173-0731-01).

953 **Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled**  
954 **Room Temperature].**

955 **MEDICATION GUIDE**

956 **WELLBUTRIN XL® (WELL byu-trin)**

957 **(bupropion hydrochloride extended-release tablets)**

958

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

963

964 **IMPORTANT: Be sure to read both sections of this Medication Guide. The first section is**  
965 **about the risk of suicidal thoughts and actions with antidepressant medicines; the second**  
966 **section is entitled “What other important information should I know about**  
967 **WELLBUTRIN XL?”**

968

969 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and**  
970 **Suicidal Thoughts or Actions**

971

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

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

977

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

- 980 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**  
981 **teenagers, and young adults within the first few months of treatment.**
- 982 **2. Depression and other serious mental illnesses are the most important causes of suicidal**  
983 **thoughts and actions. Some people may have a particularly high risk of having suicidal**

984 **thoughts or actions.** These include people who have (or have a family history of) bipolar  
985 illness (also called manic-depressive illness) or suicidal thoughts or actions.

986 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**  
987 **family member?**

- 988 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,  
989 thoughts, or feelings. This is very important when an antidepressant medicine is started or  
990 when the dose is changed.
- 991 • Call the healthcare provider right away to report new or sudden changes in mood,  
992 behavior, thoughts, or feelings.
- 993 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare  
994 provider between visits as needed, especially if you have concerns about symptoms.

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

- 998 • thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

999

1000 **What else do I need to know about antidepressant medicines?**

- 1001 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**  
1002 Stopping an antidepressant medicine suddenly can cause other symptoms.
- 1003 • **Antidepressants are medicines used to treat depression and other illnesses.** It is  
1004 important to discuss all the risks of treating depression and also the risks of not treating it.  
1005 Patients and their families or other caregivers should discuss all treatment choices with the  
1006 healthcare provider, not just the use of antidepressants.
- 1007 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the  
1008 side effects of the medicine prescribed for you or your family member.
- 1009 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines  
1010 that you or your family member takes. Keep a list of all medicines to show the healthcare  
1011 provider. Do not start new medicines without first checking with your healthcare provider.
- 1012 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**  
1013 **children.** Talk to your child's healthcare provider for more information.

1014

1015 WELLBUTRIN XL has not been studied in children under the age of 18 and is not approved for  
1016 use in children and teenagers.

1017

1018 **What other important information should I know about WELLBUTRIN XL?**

1019

1020 **There is a chance of having a seizure (convulsion, fit) with WELLBUTRIN XL, especially**  
1021 **in people:**

- 1022 • with certain medical problems.
- 1023 • who take certain medicines.

1024

1025 The chance of having seizures increases with higher doses of WELLBUTRIN XL. For more  
1026 information, see the sections “Who should not take WELLBUTRIN XL?” and “What should I  
1027 tell my doctor before using WELLBUTRIN XL?” Tell your doctor about all of your medical  
1028 conditions and all the medicines you take. **Do not take any other medicines while you are**  
1029 **using WELLBUTRIN XL unless your doctor has said it is okay to take them.**

1030

1031 **If you have a seizure while taking WELLBUTRIN XL, stop taking the tablets and call your**  
1032 **doctor right away.** Do not take WELLBUTRIN XL again if you have a seizure.

1033

1034 **What is WELLBUTRIN XL?**

1035 WELLBUTRIN XL is a prescription medicine used to treat adults with a certain type of  
1036 depression called major depressive disorder and for prevention of autumn-winter seasonal  
1037 depression (seasonal affective disorder).

1038

1039 **Who should not take WELLBUTRIN XL?**

1040 **Do not take WELLBUTRIN XL if you:**

- 1041 • have or had a seizure disorder or epilepsy.
- 1042 • **are taking ZYBAN<sup>®</sup> (used to help people stop smoking) or any other medicines that**  
1043 **contain bupropion hydrochloride, such as WELLBUTRIN<sup>®</sup> Tablets or**  
1044 **WELLBUTRIN SR<sup>®</sup> Sustained-Release Tablets.** Bupropion is the same active ingredient  
1045 that is in WELLBUTRIN XL.
- 1046 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
1047 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1048 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
1049 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
1050 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 1051 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1052 • are allergic to the active ingredient in WELLBUTRIN XL, bupropion, or to any of the  
1053 inactive ingredients. See the end of this leaflet for a complete list of ingredients in  
1054 WELLBUTRIN XL.

1055

1056 **What should I tell my doctor before using WELLBUTRIN XL?**

- 1057 • **Tell your doctor about your medical conditions.** Tell your doctor if you:

- 1058 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN XL can  
1059 harm your unborn baby. If you can use WELLBUTRIN XL while you are pregnant, talk  
1060 to your doctor about how you can be on the Bupropion Pregnancy Registry.
- 1061 • **are breastfeeding.** WELLBUTRIN XL passes through your milk. It is not known if  
1062 WELLBUTRIN XL can harm your baby.
- 1063 • **have liver problems,** especially cirrhosis of the liver.
- 1064 • have kidney problems.
- 1065 • have an eating disorder such as anorexia nervosa or bulimia.
- 1066 • have had a head injury.
- 1067 • have had a seizure (convulsion, fit).
- 1068 • have a tumor in your nervous system (brain or spine).
- 1069 • have had a heart attack, heart problems, or high blood pressure.
- 1070 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1071 • drink a lot of alcohol.
- 1072 • abuse prescription medicines or street drugs.
- 1073 • **Tell your doctor about all the medicines you take,** including prescription and non-  
1074 prescription medicines, vitamins and herbal supplements. Many medicines increase your  
1075 chances of having seizures or other serious side effects if you take them while you are using  
1076 WELLBUTRIN XL.
- 1077

#### 1078 **How should I take WELLBUTRIN XL?**

- 1079 • Take WELLBUTRIN XL exactly as prescribed by your doctor.
- 1080 • **Do not chew, cut, or crush WELLBUTRIN XL tablets.** You must swallow the tablets  
1081 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 1082 • Take WELLBUTRIN XL at the same time each day.
- 1083 • Take your doses of WELLBUTRIN XL at least 24 hours apart.
- 1084 • You may take WELLBUTRIN XL with or without food.
- 1085 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and  
1086 take your next tablet at the regular time. **This is very important.** Too much  
1087 WELLBUTRIN XL can increase your chance of having a seizure.
- 1088 • If you take too much WELLBUTRIN XL, or overdose, call your local emergency room or  
1089 poison control center right away.
- 1090 • The WELLBUTRIN XL tablet is covered by a shell that slowly releases the medicine inside  
1091 your body. You may notice something in your stool that looks like a tablet. This is normal.  
1092 This is the empty shell passing from your body.
- 1093 • **Do not take any other medicines while using WELLBUTRIN XL unless your doctor has**  
1094 **told you it is okay.**
- 1095 • If you are taking WELLBUTRIN XL for the treatment of major depressive disorder, it may  
1096 take several weeks for you to feel that WELLBUTRIN XL is working. Once you feel better,



1097 it is important to keep taking WELLBUTRIN XL exactly as directed by your doctor. Call  
1098 your doctor if you do not feel WELLBUTRIN XL is working for you.  
1099 • If you are taking WELLBUTRIN XL for the prevention of seasonal major depressive  
1100 episodes associated with seasonal affective disorder, it is important to keep taking  
1101 WELLBUTRIN XL through the autumn-winter season, or as directed by your doctor.  
1102 • Do not change your dose or stop taking WELLBUTRIN XL without talking with your doctor  
1103 first.

1104

#### 1105 **What should I avoid while taking WELLBUTRIN XL?**

- 1106 • Do not drink a lot of alcohol while taking WELLBUTRIN XL. If you usually drink a lot of  
1107 alcohol, talk with your doctor before suddenly stopping. If you suddenly stop drinking  
1108 alcohol, you may increase your chance of having seizures.
- 1109 • Do not drive a car or use heavy machinery until you know how WELLBUTRIN XL affects  
1110 you. WELLBUTRIN XL can impair your ability to perform these tasks.

1111

#### 1112 **What are possible side effects of WELLBUTRIN XL?**

- 1113 • **Seizures.** Some patients get seizures while taking WELLBUTRIN XL. **If you have a seizure**  
1114 **while taking WELLBUTRIN XL, stop taking the tablets and call your doctor right**  
1115 **away.** Do not take WELLBUTRIN XL again if you have a seizure.
- 1116 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
1117 severe, while taking WELLBUTRIN XL. The chance of high blood pressure may be  
1118 increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help  
1119 you stop smoking.
- 1120 • **Severe allergic reactions. Stop taking WELLBUTRIN XL and call your doctor right**  
1121 **away** if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the  
1122 mouth or around the eyes, swelling of the lips or tongue, chest pain, or have trouble  
1123 breathing. These could be signs of a serious allergic reaction.
- 1124 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1125 taking WELLBUTRIN XL, including delusions (believe you are someone else),  
1126 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are  
1127 against you), or feeling confused. If this happens to you, call your doctor.

1128

1129 Common side effects reported in studies of major depressive disorder include weight loss, loss of  
1130 appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation,  
1131 anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating  
1132 more often. In studies of seasonal affective disorder, common side effects included weight loss,  
1133 constipation, and gas.

1134

1135 If you have nausea, take your medicine with food. If you have trouble sleeping, do not take your  
1136 medicine too close to bedtime.

1137

1138 Tell your doctor right away about any side effects that bother you.

1139

1140 These are not all the side effects of WELLBUTRIN XL. For a complete list, ask your doctor or  
1141 pharmacist.

1142

1143 **How should I store WELLBUTRIN XL?**

- 1144 • Store WELLBUTRIN XL at room temperature. Store out of direct sunlight. Keep  
1145 WELLBUTRIN XL in its tightly closed bottle.
- 1146 • WELLBUTRIN XL tablets may have an odor.

1147

1148 **General Information about WELLBUTRIN XL.**

- 1149 • Medicines are sometimes prescribed for purposes other than those listed in a Medication  
1150 Guide. Do not use WELLBUTRIN XL for a condition for which it was not prescribed. Do  
1151 not give WELLBUTRIN XL to other people, even if they have the same symptoms you have.  
1152 It may harm them. Keep WELLBUTRIN XL out of the reach of children.

1153

1154 This Medication Guide summarizes important information about WELLBUTRIN XL. For more  
1155 information, talk with your doctor. You can ask your doctor or pharmacist for information about  
1156 WELLBUTRIN XL that is written for health professionals or you can visit  
1157 [www.wellbutrin-xl.com](http://www.wellbutrin-xl.com) or call toll-free 888-825-5249.

1158

1159 **What are the ingredients in WELLBUTRIN XL?**

1160 Active ingredient: bupropion hydrochloride.

1161

1162 Inactive ingredients: ethylcellulose aqueous dispersion (NF), glyceryl behenate, methacrylic acid  
1163 copolymer dispersion (NF), polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide,  
1164 and triethyl citrate. The tablets are printed with edible black ink.

1165

1166 \*The following are registered trademarks of their respective manufacturers: NARDIL<sup>®</sup>/Warner  
1167 Lambert Company; MARPLAN<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

1168

1169 **Rx Only**

1170

1171 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1172

1173 June 2007

WXL:4MG

1174

1175 Manufactured by:  
1176 Biovail Corporation

1177 Mississauga, ON L5N 8M5, Canada for  
1178



1179  
1180 GlaxoSmithKline  
1181 Research Triangle Park, NC 27709  
1182  
1183 ©2007, GlaxoSmithKline. All rights reserved.  
1184 June 2007

WXL:2PI