

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-515/S-007

FINAL PRINTED LABELING

1 PRESCRIBING INFORMATION

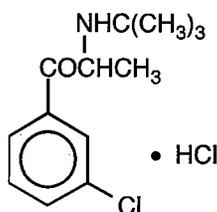
2 **WELLBUTRIN XL™**

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

4
5 **“Patient Information” enclosed.**

6 **DESCRIPTION**

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



16
17
18 WELLBUTRIN XL Tablets are supplied for oral administration as 150-mg and 300-mg,
19 creamy-white to pale yellow extended-release tablets. Each tablet contains the labeled amount of
20 bupropion hydrochloride and the inactive ingredients: ethylcellulose aqueous dispersion (NF),
21 glyceryl behenate, methacrylic acid copolymer dispersion (NF), polyvinyl alcohol, polyethylene
22 glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black
23 ink.

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

26 **CLINICAL PHARMACOLOGY**

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

31 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and
32 pharmacokinetics of the individual enantiomers have not been studied. The mean elimination
33 half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma
34 concentrations of bupropion are reached within 8 days.

35 In a study comparing 14-day dosing with WELLBUTRIN XL Tablets 300 mg once daily to
36 the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was
37 demonstrated for peak plasma concentration and area under the curve for bupropion and the
38 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion).

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

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

46 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been
47 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group
48 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,
49 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome
50 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,
51 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.
52 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of
53 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency
54 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,
55 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is
56 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are
57 5-fold less potent than bupropion. This may be of clinical importance because the plasma
58 concentrations of the metabolites are as high or higher than those of bupropion.

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

64 In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours
65 after administration of WELLBUTRIN XL. Following administration of WELLBUTRIN XL,
66 peak plasma concentrations of hydroxybupropion are approximately 7 times the peak level of the
67 parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20
68 (± 5) hours, and its AUC at steady state is about 13 times that of bupropion. The times to peak
69 concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar
70 to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer,
71 approximately 33 (± 10) and 37 (± 13) hours, respectively, and steady-state AUCs are 1.4 and
72 7 times that of bupropion, respectively.

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

75 **Elimination:** Following oral administration of 200 mg of ¹⁴C-bupropion in humans, 87% and
76 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the
77 fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent
78 with the extensive metabolism of bupropion.

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

85 **Hepatic:** The effect of hepatic impairment on the pharmacokinetics of bupropion was
86 characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in
87 patients with mild to severe cirrhosis. The first study showed that the half-life of
88 hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in
89 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically
90 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
91 greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for
92 bupropion and the other metabolites in the 2 patient groups were minimal.

93 The second study showed no statistically significant differences in the pharmacokinetics of
94 bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis
95 compared to 8 healthy volunteers. However, more variability was observed in some of the
96 pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites (t_{1/2})
97 in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic
98 cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by
99 approximately 70% and 3-fold, respectively) and more variable when compared to values in
100 healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with
101 severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion,
102 the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers
103 threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower.
104 The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for
105 threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for
106 hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for
107 hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively,
108 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,
109 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

110 **Renal:** The effect of renal disease on the pharmacokinetics of bupropion has not been
111 studied. The elimination of the major metabolites of bupropion may be affected by reduced renal
112 function.

113 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in
114 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on

115 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed,
116 compared to healthy volunteers.

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

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

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

134 **CLINICAL TRIALS**

135 The efficacy of bupropion as a treatment for major depressive disorder was established with
136 the immediate-release formulation of bupropion in two 4-week, placebo-controlled trials in adult
137 inpatients and in one 6-week, placebo-controlled trial in adult outpatients. In the first study,
138 patients were titrated in a bupropion dose range of 300 to 600 mg/day of the immediate-release
139 formulation on a 3 times daily schedule; 78% of patients received maximum doses of
140 450 mg/day or less. This trial demonstrated the effectiveness of bupropion on the Hamilton
141 Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale,
142 and the Clinical Global Impressions (CGI) severity score. A second study included 2 fixed doses
143 of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial
144 demonstrated the effectiveness of bupropion, but only at the 450-mg/day dose of the
145 immediate-release formulation; the results were positive for the HDRS total score and the CGI
146 severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of
147 the immediate-release formulation of bupropion. This study demonstrated the effectiveness of
148 bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating
149 Scale, the CGI severity score, and the CGI improvement score.

150 Although there are no independent trials demonstrating the antidepressant effectiveness of
151 WELLBUTRIN XL, studies have demonstrated similar bioavailability of the immediate-release
152 and the extended-release formulations of bupropion under steady-state conditions, i.e.,
153 WELLBUTRIN XL 300 mg once daily was shown to have bioavailability that was similar to that

154 of 100 mg 3 times daily of the immediate-release formulation of bupropion, with regard to both
155 rate and extent of absorption, for parent drug and metabolites.

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

165 **INDICATIONS AND USAGE**

166 WELLBUTRIN XL is indicated for the treatment of major depressive disorder.

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

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

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

183 **CONTRAINDICATIONS**

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

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

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

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

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

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

200 **WARNINGS**

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

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

210 WELLBUTRIN XL should be discontinued and not restarted in patients who experience a
211 seizure while on treatment.

212 As both WELLBUTRIN XL and the sustained-release formulation of bupropion
213 (WELLBUTRIN SR) are bioequivalent to the immediate-release formulation of bupropion,
214 the seizure incidence with WELLBUTRIN XL, while not formally evaluated in clinical
215 trials, may be similar to that presented below for the immediate-release and
216 sustained-release formulations of bupropion.

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

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

223 Additional data accumulated for the immediate-release formulation of bupropion
224 suggested that the estimated seizure incidence increases almost tenfold between 450 and
225 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the
226 maximum recommended daily dose (450 mg) of WELLBUTRIN XL Tablets. This
227 disproportionate increase in seizure incidence with dose incrementation calls for
228 caution in dosing.

229 • **Patient factors:** Predisposing factors that may increase the risk of seizure with
230 bupropion use include history of head trauma or prior seizure, central nervous system

231 (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications
232 that lower seizure threshold.

- 233 • **Clinical situations:** Circumstances associated with an increased seizure risk include,
234 among others, excessive use of alcohol or sedatives (including benzodiazepines);
235 addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and
236 anorectics; and diabetes treated with oral hypoglycemics or insulin.
- 237 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,
238 theophylline, systemic steroids) are known to lower seizure threshold.

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

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

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

248 **Hepatic Impairment:** WELLBUTRIN XL should be used with extreme caution in patients
249 with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required,
250 as peak bupropion, as well as AUC, levels are substantially increased and accumulation is
251 likely to occur in such patients to a greater extent than usual. The dose should not exceed
252 150 mg every other day in these patients (see CLINICAL PHARMACOLOGY,
253 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

258 **Clinical Worsening and Suicide Risk:** Patients with major depressive disorder, both adult
259 and pediatric, may experience worsening of their depression and/or the emergence of suicidal
260 ideation and behavior (suicidality), whether or not they are taking antidepressant medications,
261 and this risk may persist until significant remission occurs. Although there has been a long-
262 standing concern that antidepressants may have a role in inducing worsening of depression and
263 the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such
264 behaviors has not been established. **Nevertheless, patients being treated with antidepressants
265 should be observed closely for clinical worsening and suicidality, especially at the beginning
266 of a course of drug therapy, or at the time of dose changes, either increases or decreases.**
267 Consideration should be given to changing the therapeutic regimen, including possibly
268 discontinuing the medication in patients whose depression is persistently worse or whose
269 emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting
270 symptoms.

271 Because of the possibility of co-morbidity between major depressive disorder and other
272 psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients
273 with major depressive disorder should be observed when treating patients with other psychiatric
274 and nonpsychiatric disorders.

275 The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility
276 (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have
277 been reported in adult and pediatric patients being treated with antidepressants for major
278 depressive disorder as well as for other indications, both psychiatric and nonpsychiatric.

279 Although a causal link between the emergence of such symptoms and either the worsening of
280 depression and/or the emergence of suicidal impulses has not been established, consideration
281 should be given to changing the therapeutic regimen, including possibly discontinuing the
282 medication in patients for whom such symptoms are severe, abrupt in onset, or were not part of
283 the patient's presenting symptoms.

284 **Families and caregivers of patients being treated with antidepressants for major**
285 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**
286 **alerted about the need to monitor patients for the emergence of agitation, irritability, and**
287 **the other symptoms described above, as well as the emergence of suicidality, and to report**
288 **such symptoms immediately to health care providers.** Prescriptions for WELLBUTRIN XL
289 should be written for the smallest quantity of tablets consistent with good patient management, in
290 order to reduce the risk of overdose.

291 It should be noted that WELLBUTRIN XL is not approved for use in treating any indications
292 in the pediatric population.

293 A major depressive episode may be the initial presentation of bipolar disorder. It is generally
294 believed (although not established in controlled trials) that treating such an episode with an
295 antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in
296 patients at risk for bipolar disorder. Whether any of the symptoms described above represent
297 such a conversion is unknown. However, prior to initiating treatment with an antidepressant,
298 patients should be adequately screened to determine if they are at risk for bipolar disorder; such
299 screening should include a detailed psychiatric history, including a family history of suicide,
300 bipolar disorder, and depression. It should be noted that WELLBUTRIN XL is not approved for
301 use in treating bipolar depression.

302 **PRECAUTIONS**

303 **General: *Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia,
304 especially shortly after initiation of treatment, have been associated with treatment with
305 bupropion. Patients in placebo-controlled trials with WELLBUTRIN SR, the sustained-release
306 formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 1.

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

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

308

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

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

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

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

322 **Altered Appetite and Weight:** In placebo-controlled studies using WELLBUTRIN SR,
323 the sustained-release formulation of bupropion, patients experienced weight gain or weight loss
324 as shown in Table 2.

325

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

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

327

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

333 **Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by symptoms such
334 as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported
335 in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing

336 reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated
337 with bupropion. A patient should stop taking WELLBUTRIN XL and consult a doctor if
338 experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives,
339 chest pain, edema, and shortness of breath) during treatment.

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

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

347 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN®
348 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of
349 sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a
350 higher incidence of treatment-emergent hypertension in patients treated with the combination of
351 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the
352 combination of sustained-release bupropion and NTS had treatment-emergent hypertension
353 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,
354 and placebo, respectively. The majority of these patients had evidence of pre-existing
355 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and
356 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension
357 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure
358 is recommended in patients who receive the combination of bupropion and nicotine replacement.

359 There is no clinical experience establishing the safety of WELLBUTRIN XL Tablets in
360 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care
361 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed
362 patients who had previously developed orthostatic hypotension while receiving tricyclic
363 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with
364 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine
365 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in
366 2 patients for exacerbation of baseline hypertension.

367 **Hepatic Impairment:** WELLBUTRIN XL should be used with extreme caution in patients
368 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.
369 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including
370 mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in
371 patients with mild to moderate hepatic cirrhosis.

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

375 **Renal Impairment:** No studies have been conducted in patients with renal impairment.
376 Bupropion is extensively metabolized in the liver to active metabolites, which are further
377 metabolized and subsequently excreted by the kidneys. WELLBUTRIN XL should be used with
378 caution in patients with renal impairment and a reduced frequency and/or dose should be
379 considered as bupropion and its metabolites may accumulate in such patients to a greater extent
380 than usual. The patient should be closely monitored for possible adverse effects that could
381 indicate high drug or metabolite levels.

382 **Information for Patients:** See the tear-off leaflet at the end of this labeling for Patient
383 Information.

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

389 Physicians are advised to discuss the following issues with patients:

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

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

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

401 Patients and their families should be encouraged to be alert to the emergence of anxiety,
402 agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania,
403 worsening of depression, and suicidal ideation, especially early during antidepressant treatment.
404 Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt
405 in onset, or were not part of the patient's presenting symptoms.

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

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

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

413 Patients should be advised that they may notice in their stool something that looks like a
414 tablet. This is normal. The medication in WELLBUTRIN XL is contained in a non-absorbable

415 shell that has been specially designed to slowly release drug in the body. When this process is
416 completed, the empty shell is eliminated from the body.

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

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

421 Because bupropion is extensively metabolized, the coadministration of other drugs may affect
422 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to
423 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug
424 interaction between WELLBUTRIN XL and drugs that are substrates or inhibitors of the
425 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro
426 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,
427 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been
428 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not
429 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant
430 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites
431 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg
432 tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine,
433 the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were
434 16% and 32% increases in the AUC and C_{max} , respectively, of the combined moieties of
435 threohydrobupropion and erythrohydrobupropion.

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

438 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
439 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to
440 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.
441 Nevertheless, there may be the potential for clinically important alterations of blood levels of
442 coadministered drugs.

443 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most
444 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are
445 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this
446 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a
447 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6
448 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of
449 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of
450 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the
451 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6
452 has not been formally studied.

453 Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6
454 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,

455 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),
456 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),
457 should be approached with caution and should be initiated at the lower end of the dose range of
458 the concomitant medication. If bupropion is added to the treatment regimen of a patient already
459 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original
460 medication should be considered, particularly for those concomitant medications with a narrow
461 therapeutic index.

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

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

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

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

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

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

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

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

492 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Teratology studies have been
493 performed with bupropion immediate-release formulation at dosages up to 450 mg/kg in rats, and
494 at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively,

495 on a mg/m² basis), and have revealed no evidence of harm to the fetus due to bupropion. There
496 are no adequate and well-controlled studies in pregnant women. Because animal reproduction
497 studies are not always predictive of human response, this drug should be used during pregnancy
498 only if clearly needed.

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

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

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

508 **Pediatric Use:** The safety and effectiveness of WELLBUTRIN XL Tablets in pediatric
509 patients below 18 years old have not been established. The immediate-release formulation of
510 bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug
511 for other indications. Although generally well tolerated, the limited exposure is insufficient to
512 assess the safety of bupropion in pediatric patients (see **WARNINGS—Clinical Worsening and**
513 **Suicide Risk**).

514 **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with
515 bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65
516 years old and 47 were ≥75 years old. In addition, several hundred patients 65 and over
517 participated in clinical trials using the immediate-release formulation of bupropion (depression
518 studies). No overall differences in safety or effectiveness were observed between these subjects
519 and younger subjects. Reported clinical experience has not identified differences in responses
520 between the elderly and younger patients, but greater sensitivity of some older individuals cannot
521 be ruled out.

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

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

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

532 WELLBUTRIN XL has been demonstrated to have similar bioavailability to the
533 immediate-release formulation of bupropion (see **CLINICAL PHARMACOLOGY**). The

534 information included under the Incidence in Controlled Trials subsection of ADVERSE
 535 REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR
 536 Tablets, the sustained-release formulation of bupropion. WELLBUTRIN XL has not been
 537 studied in placebo-controlled trials, although it has been studied in non-placebo-controlled
 538 clinical bioavailability studies. Information on additional adverse events associated with the
 539 sustained-release formulation of bupropion in smoking cessation trials, as well as the
 540 immediate-release formulation of bupropion, is included in a separate section (see Other Events
 541 Observed During the Clinical Development and Postmarketing Experience of Bupropion).
 542 **Incidence in Controlled Trials With Bupropion: Adverse Events Associated With**
 543 **Discontinuation of Treatment Among Patients Treated With Bupropion:** In
 544 placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day,
 545 respectively, of the sustained-release formulation of bupropion and 4% of patients treated with
 546 placebo discontinued treatment due to adverse events. The specific adverse events in these trials
 547 that led to discontinuation in at least 1% of patients treated with either 300 mg/day or
 548 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of bupropion, and at a rate
 549 at least twice the placebo rate are listed in Table 3.

550

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

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

552

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

557 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**
 558 **Treated With Bupropion:** Table 4 enumerates treatment-emergent adverse events that
 559 occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of
 560 bupropion and with placebo in controlled trials. Events that occurred in either the 300- or
 561 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo
 562 group are included. Reported adverse events were classified using a COSTART-based
 563 Dictionary.

564 Accurate estimates of the incidence of adverse events associated with the use of any drug are
 565 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician
 566 judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward

567 events in the course of usual medical practice where patient characteristics and other factors
568 differ from those that prevailed in the clinical trials. These incidence figures also cannot be
569 compared with those obtained from other clinical studies involving related drug products as each
570 group of drug trials is conducted under a different set of conditions.

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

575

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

Body System/ Adverse Event	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%

Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage [†]	0%	2%	—
Urinary tract infection	1%	0%	—

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

582 † Incidence based on the number of female patients.

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

584

585 Additional events to those listed in Table 4 that occurred at an incidence of at least 1% in
586 controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day)
587 and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%),
588 hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase
589 (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%),
590 impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%),

591 decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and
592 gustatory disturbance (3% vs 1%).

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

594 Adverse events from Table 4 occurring in at least 5% of patients treated with the
595 sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed
596 below for the 300- and 400-mg/day dose groups.

597 ***300 mg/day of the Sustained-Release Formulation:*** Anorexia, dry mouth, rash,
598 sweating, tinnitus, and tremor.

599 ***400 mg/day of the Sustained-Release Formulation:*** Abdominal pain, agitation,
600 anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating,
601 tinnitus, and urinary frequency.

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

603 **Experience of Bupropion:** In addition to the adverse events noted above, the following
604 events have been reported in clinical trials and postmarketing experience with the
605 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,
606 as well as in clinical trials and postmarketing clinical experience with the immediate-release
607 formulation of bupropion.

608 Adverse events for which frequencies are provided below occurred in clinical trials with the
609 sustained-release formulation of bupropion. The frequencies represent the proportion of patients
610 who experienced a treatment-emergent adverse event on at least one occasion in
611 placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients
612 who experienced an adverse event requiring discontinuation of treatment in an open-label
613 surveillance study with the sustained-release formulation of bupropion (n = 3,100). All
614 treatment-emergent adverse events are included except those listed in Tables 1 through 4, those
615 events listed in other safety-related sections, those adverse events subsumed under COSTART
616 terms that are either overly general or excessively specific so as to be uninformative, those
617 events not reasonably associated with the use of the drug, and those events that were not serious
618 and occurred in fewer than 2 patients. Events of major clinical importance are described in the
619 WARNINGS and PRECAUTIONS sections of the labeling.

620 Events are further categorized by body system and listed in order of decreasing frequency
621 according to the following definitions of frequency: Frequent adverse events are defined as those
622 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
623 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

628 ***Body (General):*** Infrequent were chills, facial edema, musculoskeletal chest pain, and
629 photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash

630 and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble
631 serum sickness (see PRECAUTIONS).

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

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

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

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

646 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed
647 was glycosuria.

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

650 **Nervous System:** Infrequent were abnormal coordination, decreased libido,
651 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
652 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also
653 observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium,
654 dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations,
655 hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and
656 unmasking tardive dyskinesia.

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

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

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

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

665 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

688 OVERDOSAGE

689 **Human Overdose Experience:** There has been very limited experience with overdosage of
690 the sustained-release formulation of bupropion (WELLBUTRIN SR Tablets); 3 cases were
691 reported during clinical trials. One patient ingested 3,000 mg of the sustained-release formulation
692 of bupropion and vomited quickly after the overdose; the patient experienced blurred vision and
693 lightheadedness. A second patient ingested a "handful" of WELLBUTRIN SR Tablets (the
694 sustained-release formulation) and experienced confusion, lethargy, nausea, jitteriness, and
695 seizure. A third patient ingested 3,600 mg of the sustained-release formulation of bupropion and
696 a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of
697 the patients experienced further sequelae.

698 There has been extensive experience with overdosage of the immediate-release formulation of
699 bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to
700 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 mg of
701 the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a
702 grand mal seizure and recovered without further sequelae.

703 Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of
704 bupropion have been reported. Seizure was reported in approximately one third of all cases.
705 Other serious reactions reported with overdoses of the immediate-release formulation of

706 bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever,
707 muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been
708 reported when the immediate-release formulation of bupropion was part of multiple drug
709 overdoses.

710 Although most patients recovered without sequelae, deaths associated with overdoses of the
711 immediate-release formulation of bupropion alone have been reported rarely in patients ingesting
712 massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and
713 cardiac arrest prior to death were reported in these patients.

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

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

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

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

731 **DOSAGE AND ADMINISTRATION**

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

740 WELLBUTRIN XL should be swallowed whole and not crushed, divided, or chewed.

741 WELLBUTRIN XL may be taken without regard to meals.

742 **Initial Treatment:** The usual adult target dose for WELLBUTRIN XL Tablets is 300 mg/day,
743 given once daily in the morning. Dosing with WELLBUTRIN XL Tablets should begin at
744 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately

745 tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early
746 as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.
747 **Increasing the Dosage Above 300 mg/day:** As with other antidepressants, the full
748 antidepressant effect of WELLBUTRIN XL Tablets may not be evident until 4 weeks of
749 treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single
750 dose, may be considered for patients in whom no clinical improvement is noted after several
751 weeks of treatment at 300 mg/day.

752 **Switching Patients from WELLBUTRIN Tablets or from WELLBUTRIN SR**
753 **Sustained-Release Tablets:** When switching patients from WELLBUTRIN Tablets to
754 WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to
755 WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently
756 being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day)
757 may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being
758 treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg
759 twice daily) may be switched to WELLBUTRIN XL 300 mg once daily.

760 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require
761 several months or longer of sustained pharmacological therapy beyond response to the acute
762 episode. It is unknown whether or not the dose of WELLBUTRIN XL needed for maintenance
763 treatment is identical to the dose needed to achieve an initial response. Patients should be
764 periodically reassessed to determine the need for maintenance treatment and the appropriate dose
765 for such treatment.

766 **Dosage Adjustment for Patients With Impaired Hepatic Function:**
767 WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic
768 cirrhosis. The dose should not exceed 150 mg every other day in these patients.
769 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including
770 mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in
771 patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY,
772 WARNINGS, and PRECAUTIONS).

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

776 HOW SUPPLIED

777 WELLBUTRIN XL Extended-Release Tablets, 150 mg of bupropion hydrochloride, are
778 creamy-white to pale yellow, round, tablets printed with "WELLBUTRIN XL 150" in bottles of
779 30 tablets (NDC 0173-0730-01).

780 WELLBUTRIN XL Extended-Release Tablets, 300 mg of bupropion hydrochloride, are
781 creamy-white to pale yellow, round, tablets printed with "WELLBUTRIN XL 300" in bottles of
782 30 tablets (NDC 0173-0731-01).

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

785



786

787 **Manufactured by:**

788 **Biovail Corporation**

789 **Mississauga, ON L5N 8M5, Canada for**

790 **GlaxoSmithKline**

791 **Research Triangle Park, NC 27709**

792

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795 **April 2004**

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