

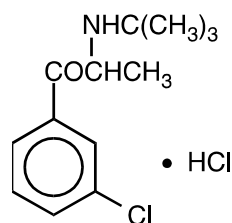
PRESCRIBING INFORMATION

1
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:
15



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 PRECAUTIONS

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

263 **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%

264

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

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

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

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

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

281

282 **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%

283

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

289 **Suicide:** The possibility of a suicide attempt is inherent in depression and may persist until
290 significant remission occurs. Accordingly, prescriptions for WELLBUTRIN XL Tablets should
291 be written for the smallest number of tablets consistent with good patient management.

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

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

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

306 Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN[®]
307 Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of
308 sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a
309 higher incidence of treatment-emergent hypertension in patients treated with the combination of
310 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the
311 combination of sustained-release bupropion and NTS had treatment-emergent hypertension
312 compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS,
313 and placebo, respectively. The majority of these patients had evidence of pre-existing
314 hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and
315 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension
316 compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure
317 is recommended in patients who receive the combination of bupropion and nicotine replacement.

318 There is no clinical experience establishing the safety of WELLBUTRIN XL Tablets in
319 patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care
320 should be exercised if it is used in these groups. Bupropion was well tolerated in depressed
321 patients who had previously developed orthostatic hypotension while receiving tricyclic
322 antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with
323 stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine
324 blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in
325 2 patients for exacerbation of baseline hypertension.

326 **Hepatic Impairment:** WELLBUTRIN XL should be used with extreme caution in patients
327 with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required.
328 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including
329 mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in
330 patients with mild to moderate hepatic cirrhosis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

375 Because bupropion is extensively metabolized, the coadministration of other drugs may affect
376 its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to
377 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug
378 interaction between WELLBUTRIN XL and drugs that are substrates or inhibitors of the
379 CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro
380 studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,
381 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been
382 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not
383 appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant
384 administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites
385 were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg
386 tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine,
387 the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were
388 16% and 32% increases in the AUC and C_{max} , respectively, of the combined moieties of
389 threohydrobupropion and erythrohydrobupropion.

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

392 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
393 humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to
394 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.
395 Nevertheless, there may be the potential for clinically important alterations of blood levels of
396 coadministered drugs.

397 **Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):** Many drugs, including most
398 antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are
399 metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this
400 isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a
401 study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6
402 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of
403 50 mg desipramine increased the C_{max} , AUC, and $t_{1/2}$ of desipramine by an average of
404 approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the
405 last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6
406 has not been formally studied.

407 Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6
408 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine,
409 paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine),
410 beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide),

411 should be approached with caution and should be initiated at the lower end of the dose range of
412 the concomitant medication. If bupropion is added to the treatment regimen of a patient already
413 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original
414 medication should be considered, particularly for those concomitant medications with a narrow
415 therapeutic index.

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

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

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

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

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

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

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

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

446 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Teratology studies have been
447 performed with bupropion immediate-release formulation at dosages up to 450 mg/kg in rats, and
448 at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively,
449 on a mg/m² basis), and have revealed no evidence of harm to the fetus due to bupropion. There
450 are no adequate and well-controlled studies in pregnant women. Because animal reproduction

451 studies are not always predictive of human response, this drug should be used during pregnancy
452 only if clearly needed.

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

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

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

462 **Pediatric Use:** The safety and effectiveness of WELLBUTRIN XL Tablets in pediatric
463 patients below 18 years old have not been established. The immediate-release formulation of
464 bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug
465 for other indications. Although generally well tolerated, the limited exposure is insufficient to
466 assess the safety of bupropion in pediatric patients.

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

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

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

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

485 WELLBUTRIN XL has been demonstrated to have similar bioavailability to the
486 immediate-release formulation of bupropion (see CLINICAL PHARMACOLOGY). The
487 information included under the Incidence in Controlled Trials subsection of ADVERSE
488 REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR
489 Tablets, the sustained-release formulation of bupropion. WELLBUTRIN XL has not been

490 studied in placebo-controlled trials, although it has been studied in non-placebo-controlled
491 clinical bioavailability studies. Information on additional adverse events associated with the
492 sustained-release formulation of bupropion in smoking cessation trials, as well as the
493 immediate-release formulation of bupropion, is included in a separate section (see Other Events
494 Observed During the Clinical Development and Postmarketing Experience of Bupropion).

495 **Incidence in Controlled Trials With Bupropion: Adverse Events Associated With**
496 **Discontinuation of Treatment Among Patients Treated With Bupropion:** In
497 placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day,
498 respectively, of the sustained-release formulation of bupropion and 4% of patients treated with
499 placebo discontinued treatment due to adverse events. The specific adverse events in these trials
500 that led to discontinuation in at least 1% of patients treated with either 300 mg/day or
501 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of bupropion, and at a rate
502 at least twice the placebo rate are listed in Table 3.

503
504

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%

505

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

510 **Adverse Events Occurring at an Incidence of 1% or More Among Patients**
511 **Treated With Bupropion:** Table 4 enumerates treatment-emergent adverse events that
512 occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of
513 bupropion and with placebo in controlled trials. Events that occurred in either the 300- or
514 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo
515 group are included. Reported adverse events were classified using a COSTART-based
516 Dictionary.

517 Accurate estimates of the incidence of adverse events associated with the use of any drug are
518 difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician
519 judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward
520 events in the course of usual medical practice where patient characteristics and other factors
521 differ from those that prevailed in the clinical trials. These incidence figures also cannot be

522 compared with those obtained from other clinical studies involving related drug products as each
523 group of drug trials is conducted under a different set of conditions.

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

528

529 **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%	—

530 * Adverse events that occurred in at least 1% of patients treated with either 300 or
531 400 mg/day of the sustained-release formulation of bupropion, but equally or more
532 frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite
533 increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome,
534 hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

535 [†] Incidence based on the number of female patients.

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

537

538 Additional events to those listed in Table 4 that occurred at an incidence of at least 1% in
539 controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day)
540 and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%),
541 hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase
542 (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%),
543 impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%),

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

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

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

550 ***300 mg/day of the Sustained-Release Formulation:*** Anorexia, dry mouth, rash,
551 sweating, tinnitus, and tremor.

552 ***400 mg/day of the Sustained-Release Formulation:*** Abdominal pain, agitation,
553 anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating,
554 tinnitus, and urinary frequency.

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

556 **Experience of Bupropion:** In addition to the adverse events noted above, the following
557 events have been reported in clinical trials and postmarketing experience with the
558 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,
559 as well as in clinical trials and postmarketing clinical experience with the immediate-release
560 formulation of bupropion.

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

573 Events are further categorized by body system and listed in order of decreasing frequency
574 according to the following definitions of frequency: Frequent adverse events are defined as those
575 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to
576 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

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

599 **Metabolic and Nutritional:** Infrequent were edema and peripheral edema. Also observed
600 was glycosuria.

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

603 **Nervous System:** Infrequent were abnormal coordination, decreased libido,
604 depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
605 suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also
606 observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium,
607 dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations,
608 hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and
609 unmasking tardive dyskinesia.

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

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

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

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

618 **DRUG ABUSE AND DEPENDENCE**

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

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

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

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

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

641 **OVERDOSAGE**

642 **Human Overdose Experience:** There has been very limited experience with overdose of
643 the sustained-release formulation of bupropion (WELLBUTRIN SR Tablets); 3 cases were
644 reported during clinical trials. One patient ingested 3,000 mg of the sustained-release formulation
645 of bupropion and vomited quickly after the overdose; the patient experienced blurred vision and
646 lightheadedness. A second patient ingested a "handful" of WELLBUTRIN SR Tablets (the
647 sustained-release formulation) and experienced confusion, lethargy, nausea, jitteriness, and
648 seizure. A third patient ingested 3,600 mg of the sustained-release formulation of bupropion and
649 a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of
650 the patients experienced further sequelae.

651 There has been extensive experience with overdose of the immediate-release formulation of
652 bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to
653 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 mg of
654 the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a
655 grand mal seizure and recovered without further sequelae.

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

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

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

667 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.
668 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first
669 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.
670 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with
671 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in
672 symptomatic patients.

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

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

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

684 **DOSAGE AND ADMINISTRATION**

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

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

694 WELLBUTRIN XL may be taken without regard to meals.

695 **Initial Treatment:** The usual adult target dose for WELLBUTRIN XL Tablets is 300 mg/day,
696 given once daily in the morning. Dosing with WELLBUTRIN XL Tablets should begin at
697 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately

698 tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early
699 as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

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

705 **Switching Patients from WELLBUTRIN Tablets or from WELLBUTRIN SR**
706 **Sustained-Release Tablets:** When switching patients from WELLBUTRIN Tablets to
707 WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to
708 WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently
709 being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day)
710 may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being
711 treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg
712 twice daily) may be switched to WELLBUTRIN XL 300 mg once daily.

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

719 **Dosage Adjustment for Patients With Impaired Hepatic Function:**
720 WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic
721 cirrhosis. The dose should not exceed 150 mg every other day in these patients.
722 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including
723 mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in
724 patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY,
725 WARNINGS, and PRECAUTIONS).

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

729 **HOW SUPPLIED**

730 WELLBUTRIN XL Extended-Release Tablets, 150 mg of bupropion hydrochloride, are
731 creamy-white to pale yellow, round, tablets printed with “WELLBUTRIN XL 150” in bottles of
732 30 tablets (NDC 0173-0730-01).

733 WELLBUTRIN XL Extended-Release Tablets, 300 mg of bupropion hydrochloride, are
734 creamy-white to pale yellow, round, tablets printed with “WELLBUTRIN XL 300” in bottles of
735 30 tablets (NDC 0173-0731-01).

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

738



739

740 Manufactured by:

741 Biovail Corporation

742 Mississauga, ON L5N 8M5, Canada for

743 GlaxoSmithKline

744 Research Triangle Park, NC 27709

745

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PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

750

751

Patient Information

752

WELLBUTRIN XL™ (WELL byu trin XL)

753

(bupropion hydrochloride extended-release tablets)

754

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

759

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

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

- 763 • with certain medical problems.
- 764 • who take certain medicines.

765

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

771

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

774

775 **What is WELLBUTRIN XL?**

776 WELLBUTRIN XL is a prescription medicine used to treat adults with a certain type of
777 depression called major depressive disorder.

778

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

780 **Do not take WELLBUTRIN XL if you**

- 781 • have or had a seizure disorder or epilepsy.
- 782 • **are taking ZYBAN (used to help people stop smoking) or any other medicines that**
783 **contain bupropion hydrochloride, such as WELLBUTRIN Tablets or WELLBUTRIN**
784 **SR Sustained-Release Tablets.** Bupropion is the same active ingredient that is in
785 WELLBUTRIN XL.
- 786 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these
787 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 788 • have taken within the last 14 days medicine for depression called a monoamine oxidase
789 inhibitor (MAOI), such as NARDIL[®] (phenelzine sulfate), PARNATE[®] (tranylcypromine
790 sulfate), or MARPLAN[®] (isocarboxazid).
- 791 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 792 • are allergic to the active ingredient in WELLBUTRIN XL, bupropion, or to any of the
793 inactive ingredients. See the end of this leaflet for a complete list of ingredients in
794 WELLBUTRIN XL.

795

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

- 797 • **Tell your doctor about your medical conditions.** Tell your doctor if you
798 • **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN XL can
799 harm your unborn baby. If you can use WELLBUTRIN XL while you are pregnant, talk
800 to your doctor about how you can be on the Bupropion Pregnancy Registry.
- 801 • **are breastfeeding.** WELLBUTRIN XL passes through your milk. It is not known if
802 WELLBUTRIN XL can harm your baby.
- 803 • **have liver problems,** especially cirrhosis of the liver.
- 804 • have kidney problems.
- 805 • have an eating disorder, such as anorexia nervosa or bulimia.
- 806 • have had a head injury.
- 807 • have had a seizure (convulsion, fit).
- 808 • have a tumor in your nervous system (brain or spine).
- 809 • have had a heart attack, heart problems, or high blood pressure.
- 810 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 811 • drink a lot of alcohol.
- 812 • abuse prescription medicines or street drugs.
- 813
- 814 • **Tell your doctor about all the medicines you take,** including prescription and non-
815 prescription medicines, vitamins and herbal supplements. Many medicines increase your
816 chances of having seizures or other serious side effects if you take them while you are using
817 WELLBUTRIN XL.

818 WELLBUTRIN XL has not been studied in children under the age of 18 years.
819

820 **How should I take WELLBUTRIN XL?**

- 821 • Take WELLBUTRIN XL exactly as prescribed by your doctor.
- 822 • **Do not chew, cut, or crush WELLBUTRIN XL tablets.** You must swallow the tablets
823 whole. **Tell your doctor if you cannot swallow medicine tablets.**
- 824 • Take WELLBUTRIN XL at the same time each day.
- 825 • Take your doses of WELLBUTRIN XL at least 24 hours apart.
- 826 • You may take WELLBUTRIN XL with or without food.
- 827 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and
828 take your next tablet at the regular time. **This is very important.** Too much WELLBUTRIN
829 XL can increase your chance of having a seizure.
- 830 • If you take too much WELLBUTRIN XL, or overdose, call your local emergency room or
831 poison control center right away.
- 832 • The WELLBUTRIN XL tablet is covered by a shell that slowly releases the medicine inside
833 your body. You may notice something in your stool that looks like a tablet. This is normal.
834 This is the empty shell passing from your body.
- 835 • **Do not take any other medicines while using WELLBUTRIN XL unless your doctor has**
836 **told you it is okay.**
- 837 • It may take several weeks for you to feel that WELLBUTRIN XL is working. Once you feel
838 better, it is important to keep taking WELLBUTRIN XL exactly as directed by your doctor.
839 Call your doctor if you do not feel WELLBUTRIN XL is working for you.
- 840 • Do not change your dose or stop taking WELLBUTRIN XL without talking with your doctor
841 first.

842
843 **What should I avoid while taking WELLBUTRIN XL?**

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

849
850 **What are possible side effects of WELLBUTRIN XL?**

- 851 • **Seizures.** Some patients get seizures while taking WELLBUTRIN XL. **If you have a seizure**
852 **while taking WELLBUTRIN XL, stop taking the tablets and call your doctor right**
853 **away.** Do not take WELLBUTRIN XL again if you have a seizure.
- 854 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes
855 severe, while taking WELLBUTRIN XL. The chance of high blood pressure may be
856 increased if you also use nicotine replacement therapy (for example, a nicotine patch) to help
857 you stop smoking.
- 858 • **Severe allergic reactions. Stop WELLBUTRIN XL and call your doctor right away if**
859 **you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or**

860 around the eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These
861 could be signs of a serious allergic reaction.

- 862 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while
863 taking WELLBUTRIN XL, including delusions (believe you are someone else),
864 hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are
865 against you), or feeling confused. If this happens to you, call your doctor.

866

867 The most common side effects of WELLBUTRIN XL are weight loss, loss of appetite, dry
868 mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety,
869 dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more
870 often.

871

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

874

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

876

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

879

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

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

884

885 **General Information about WELLBUTRIN XL.**

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

891

892 This leaflet summarizes important information about WELLBUTRIN XL. For more information,
893 talk with your doctor. You can ask your doctor or pharmacist for information about
894 WELLBUTRIN XL that is written for health professionals or you can visit

895 www.wellbutrin-xl.com or call toll-free 888-825-5249.

896

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

898 Active ingredient: bupropion hydrochloride.

899

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

903

904 **R_x only**

905

906  **GlaxoSmithKline**

907 Manufactured by:

908 Biovail Corporation

909 Mississauga, ON L5N 8M5, Canada for

910 GlaxoSmithKline

911 Research Triangle Park, NC 27709

912

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