

PRESCRIBING INFORMATION

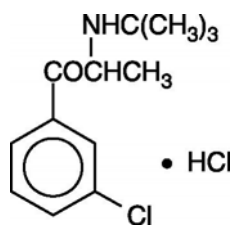
**ZYBAN<sup>®</sup>**  
**(bupropion hydrochloride)**  
**Sustained-Release Tablets**

**Suicidality and Antidepressant Drugs**

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

**DESCRIPTION**

ZYBAN (bupropion hydrochloride) Sustained-Release Tablets are a non-nicotine aid to smoking cessation. ZYBAN is chemically unrelated to nicotine or other agents currently used in the treatment of nicotine addiction. Initially developed and marketed as an antidepressant (WELLBUTRIN [bupropion hydrochloride] Tablets and WELLBUTRIN SR [bupropion hydrochloride] Sustained-Release Tablets), ZYBAN is also chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C<sub>13</sub>H<sub>18</sub>ClNO•HCl. Bupropion hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



37  
38

39 ZYBAN Tablets are supplied for oral administration as 150-mg (purple), film-coated,  
40 sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride  
41 and the inactive ingredients carnauba wax, cysteine hydrochloride, hypromellose, magnesium  
42 stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide and  
43 is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake  
44 and FD&C Red No. 40 Lake.

## 45 CLINICAL PHARMACOLOGY

46 **Pharmacodynamics:** Bupropion is a relatively weak inhibitor of the neuronal uptake of  
47 norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of  
48 serotonin. The mechanism by which ZYBAN enhances the ability of patients to abstain from  
49 smoking is unknown. However, it is presumed that this action is mediated by noradrenergic  
50 and/or dopaminergic mechanisms.

51 **Pharmacokinetics:** Bupropion is a racemic mixture. The pharmacologic activity and  
52 pharmacokinetics of the individual enantiomers have not been studied. Bupropion follows  
53 biphasic pharmacokinetics best described by a 2-compartment model. The terminal phase has a  
54 mean half-life ( $\pm$ % CV) of about 21 hours ( $\pm$ 20%), while the distribution phase has a mean  
55 half-life of 3 to 4 hours.

56 **Absorption:** Bupropion has not been administered intravenously to humans; therefore, the  
57 absolute bioavailability of ZYBAN Sustained-Release Tablets in humans has not been  
58 determined. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

59 Following oral administration of ZYBAN to healthy volunteers, peak plasma concentrations  
60 of bupropion are achieved within 3 hours. The mean peak concentration ( $C_{\max}$ ) values were  
61 91 and 143 ng/mL from 2 single-dose (150-mg) studies. At steady state, the mean  $C_{\max}$  following  
62 a 150-mg dose every 12 hours is 136 ng/mL.

63 In a single-dose study, food increased the  $C_{\max}$  of bupropion by 11% and the extent of  
64 absorption as defined by area under the plasma concentration-time curve (AUC) by 17%. The  
65 mean time to peak concentration ( $T_{\max}$ ) was prolonged by 1 hour. This effect was of no clinical  
66 significance.

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

71 distribution ( $V_{ss}/F$ ) estimated from a single 150-mg dose given to 17 subjects is 1,950 L  
72 (20% CV).

73 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
74 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
75 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
76 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
77 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
78 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
79 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of  
80 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency  
81 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,  
82 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is  
83 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are  
84 5-fold less potent than bupropion. This may be of clinical importance because the plasma  
85 concentrations of the metabolites are as high or higher than those of bupropion.

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

91 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur  
92 approximately 6 hours after administration of ZYBAN Tablets. Peak plasma concentrations of  
93 hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state.  
94 The elimination half-life of hydroxybupropion is approximately 20 ( $\pm 5$ ) hours, and its AUC at  
95 steady state is about 17 times that of bupropion. The times to peak concentrations for the  
96 erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the  
97 hydroxybupropion metabolite; however, their elimination half-lives are longer, 33 ( $\pm 10$ ) and  
98 37 ( $\pm 13$ ) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,  
99 respectively.

100 Bupropion and its metabolites exhibit linear kinetics following chronic administration of  
101 300 to 450 mg/day.

102 **Elimination:** The mean ( $\pm$ % CV) apparent clearance (Cl/F) estimated from 2 single-dose  
103 (150-mg) studies are 135 ( $\pm 20$ %) and 209 L/hr ( $\pm 21$ %). Following chronic dosing of 150 mg of  
104 ZYBAN every 12 hours for 14 days ( $n = 34$ ), the mean Cl/F at steady state was 160 L/hr ( $\pm 23$ %).  
105 The mean elimination half-life of bupropion estimated from a series of studies is approximately  
106 21 hours. Estimates of the half-lives of the metabolites determined from a multiple-dose study  
107 were 20 hours ( $\pm 25$ %) for hydroxybupropion, 37 hours ( $\pm 35$ %) for threohydrobupropion, and  
108 33 hours ( $\pm 30$ %) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion  
109 and metabolites are reached within 5 and 8 days, respectively.

110 Following oral administration of 200 mg of <sup>14</sup>C-bupropion in humans, 87% and 10% of the  
111 radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose  
112 of bupropion excreted unchanged was only 0.5%.

113 The effects of cigarette smoking on the pharmacokinetics of bupropion were studied in  
114 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were  
115 nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there was no  
116 statistically significant difference in C<sub>max</sub>, half-life, T<sub>max</sub>, AUC, or clearance of bupropion or its  
117 major metabolites between smokers and nonsmokers.

118 In a study comparing the treatment combination of ZYBAN and nicotine transdermal system  
119 (NTS) versus ZYBAN alone, no statistically significant differences were observed between the  
120 2 treatment groups of combination ZYBAN and NTS (n = 197) and ZYBAN alone (n = 193) in  
121 the plasma concentrations of bupropion or its active metabolites at weeks 3 and 6.

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

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

136 The second study showed that there were no statistically significant differences in the  
137 pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate  
138 hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in  
139 some of the pharmacokinetic parameters for bupropion (AUC, C<sub>max</sub>, and T<sub>max</sub>) and its active  
140 metabolites (t<sub>1/2</sub>) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with  
141 severe hepatic cirrhosis, the bupropion C<sub>max</sub> and AUC were substantially increased (mean  
142 difference: by approximately 70% and 3-fold, respectively) and more variable when compared to  
143 values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients  
144 with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite  
145 hydroxybupropion, the mean C<sub>max</sub> was approximately 69% lower. For the combined amino-  
146 alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C<sub>max</sub> was  
147 approximately 31% lower. The mean AUC increased by 28% for hydroxybupropion and 50% for  
148 threo/erythrohydrobupropion. The median T<sub>max</sub> was observed 19 hours later for  
149 hydroxybupropion and 21 hours later for threo/erythrohydrobupropion. The mean half-lives for

150 hydroxybupropion and threo/erythrohydrobupropion were increased 2- and 4-fold, respectively,  
151 in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS,  
152 PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

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

160 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in  
161 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on  
162 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to  
163 healthy normal volunteers, was revealed.

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

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

## 176 **CLINICAL TRIALS**

177 The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in  
178 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers ( $n = 1,940$ ,  
179  $\geq 15$  cigarettes per day). In these studies, ZYBAN was used in conjunction with individual  
180 smoking cessation counseling.

181 The first study was a dose-response trial conducted at 3 clinical centers. Patients in this study  
182 were treated for 7 weeks with 1 of 3 doses of ZYBAN (100, 150, or 300 mg/day) or placebo;  
183 quitting was defined as total abstinence during the last 4 weeks of treatment (weeks 4 through 7).  
184 Abstinence was determined by patient daily diaries and verified by carbon monoxide levels in  
185 expired air.

186 Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase in  
187 the percentage of patients able to achieve 4-week abstinence (weeks 4 through 7). Treatment

188 with ZYBAN at both 150 and 300 mg/day was significantly more effective than placebo in this  
189 study.

190 Table 1 presents quit rates over time in the multicenter trial by treatment group. The quit rates  
191 are the proportions of all persons initially enrolled (i.e., intent to treat analysis) who abstained  
192 from week 4 of the study through the specified week. Treatment with ZYBAN (150 or  
193 300 mg/day) was more effective than placebo in helping patients achieve 4-week abstinence. In  
194 addition, treatment with ZYBAN (7 weeks at 300 mg/day) was more effective than placebo in  
195 helping patients maintain continuous abstinence through week 26 (6 months) of the study.  
196

197 **Table 1. Dose-Response Trial: Quit Rates by Treatment Group**

Abstinence From Week 4 Through Specified Week	Treatment Groups			
	Placebo (n = 151) % (95% CI)	ZYBAN 100 mg/day (n = 153) % (95% CI)	ZYBAN 150 mg/day (n = 153) % (95% CI)	ZYBAN 300 mg/day (n = 156) % (95% CI)
Week 7 (4-week quit)	17% (11-23)	22% (15-28)	27%* (20-35)	36%* (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25%* (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19%* (13-25)

198 \*Significantly different from placebo ( $p \leq 0.05$ ).  
199

200 The second study was a comparative trial conducted at 4 clinical centers. Four treatments  
201 were evaluated: ZYBAN 300 mg/day, nicotine transdermal system (NTS) 21 mg/day,  
202 combination of ZYBAN 300 mg/day plus NTS 21 mg/day, and placebo. Patients were treated for  
203 9 weeks. Treatment with ZYBAN was initiated at 150 mg/day while the patient was still  
204 smoking and was increased after 3 days to 300 mg/day given as 150 mg twice daily. NTS  
205 21 mg/day was added to treatment with ZYBAN after approximately 1 week when the patient  
206 reached the target quit date. During weeks 8 and 9 of the study, NTS was tapered to 14 and  
207 7 mg/day, respectively. Quitting, defined as total abstinence during weeks 4 through 7, was  
208 determined by patient daily diaries and verified by expired air carbon monoxide levels. In this  
209 study, patients treated with any of the 3 treatments achieved greater 4-week abstinence rates than  
210 patients treated with placebo.

211 Table 2 presents quit rates over time by treatment group for the comparative trial.  
212

213 **Table 2. Comparative Trial: Quit Rates by Treatment Group**

	Treatment Groups			
	Placebo (n = 160) % (95% CI)	Nicotine Transdermal System (NTS) 21 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day (n = 244) % (95% CI)	ZYBAN 300 mg/day and NTS 21 mg/day (n = 245) % (95% CI)
Abstinence From Week 4 Through Specified Week				
Week 7 (4-week quit)	23% (17-30)	36% (30-42)	49% (43-56)	58% (51-64)
Week 10	20% (14-26)	32% (26-37)	46% (39-52)	51% (45-58)

214

215 When patients in this study were followed out to one year, the superiority of ZYBAN and the  
216 combination of ZYBAN and NTS over placebo in helping patients to achieve abstinence from  
217 smoking was maintained. The continuous abstinence rate was 30% (95% CI 24-35) in the  
218 ZYBAN treated patients, and 33% (95% CI 27-39) for patients treated with the combination at  
219 26 weeks compared with 13% (95% CI 7-18) in the placebo group. At 52 weeks, the continuous  
220 abstinence rate was 23% (95% CI 18-28) in the ZYBAN treated patients, and 28% (95% CI  
221 23-34) for patients treated with the combination, compared with 8% (95% CI 3-12) in the  
222 placebo group. Although the treatment combination of ZYBAN and NTS displayed the highest  
223 rates of continuous abstinence throughout the study, the quit rates for the combination were not  
224 significantly higher ( $p>0.05$ ) than for ZYBAN alone.

225 The comparisons between ZYBAN, NTS, and combination treatment in this study have not  
226 been replicated, and, therefore should not be interpreted as demonstrating the superiority of any  
227 of the active treatment arms over any other.

228 The third study was a long-term maintenance trial conducted at 5 clinical centers. Patients in  
229 this study received open-label ZYBAN 300 mg/day for 7 weeks. Patients who quit smoking  
230 while receiving ZYBAN (n = 432) were then randomized to ZYBAN 300 mg/day or placebo for  
231 a total study duration of 1 year. Abstinence from smoking was determined by patient self-report  
232 and verified by expired air carbon monoxide levels. This trial demonstrated that at 6 months,  
233 continuous abstinence rates were significantly higher for patients continuing to receive ZYBAN  
234 than for those switched to placebo ( $p<0.05$ ; 55% versus 44%).

235 Quit rates in clinical trials are influenced by the population selected. Quit rates in an  
236 unselected population may be lower than the above rates. Quit rates for ZYBAN were similar in  
237 patients with and without prior quit attempts using nicotine replacement therapy.

238 Treatment with ZYBAN reduced withdrawal symptoms compared to placebo. Reductions on  
239 the following withdrawal symptoms were most pronounced: irritability, frustration, or anger;  
240 anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending

241 on the study and the measure used, treatment with ZYBAN showed evidence of reduction in  
242 craving for cigarettes or urge to smoke compared to placebo.

243 **Use In Patients With Chronic Obstructive Pulmonary Disease (COPD):** ZYBAN was  
244 evaluated in a randomized, double-blind, comparative study of 404 patients with mild-to-  
245 moderate COPD, defined as  $FEV_1 \geq 35\%$ ,  $FEV_1/FVC \leq 70\%$  and a diagnosis of chronic bronchitis,  
246 emphysema and/or small airways disease. Patients aged 36 to 76 years were randomized to  
247 ZYBAN 300 mg/day (n = 204) or placebo (n = 200) and treated for 12 weeks. Treatment with  
248 ZYBAN was initiated at 150 mg/day for 3 days while the patient was still smoking and increased  
249 to 150 mg twice daily for the remaining treatment period. Abstinence from smoking was  
250 determined by patient daily diaries and verified by carbon monoxide levels in expired air.  
251 Quitters are defined as subjects who were abstinent during the last 4 weeks of treatment. Table 3  
252 shows quit rates in the COPD Trial.

253

254 **Table 3. COPD Trial: Quit Rates by Treatment Group**

	Treatment Groups	
	Placebo (n = 200) % (95% CI)	ZYBAN 300 mg/day (n = 204) % (95% CI)
4-Week Abstinence Period		
Weeks 9 through 12	12% (8-16)	22%* (17-27)

255 \*Significantly different from placebo ( $p < 0.05$ ).

## 256 INDICATIONS AND USAGE

257 ZYBAN is indicated as an aid to smoking cessation treatment.

## 258 CONTRAINDICATIONS

259 ZYBAN is contraindicated in patients with a seizure disorder.

260 ZYBAN is contraindicated in patients treated with WELLBUTRIN (bupropion  
261 hydrochloride), the immediate-release formulation; WELLBUTRIN SR (bupropion  
262 hydrochloride), the sustained-release formulation; WELLBUTRIN XL (bupropion  
263 hydrochloride), the extended-release formulation; or any other medications that contain  
264 bupropion because the incidence of seizure is dose dependent.

265 ZYBAN is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia  
266 nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the  
267 immediate-release formulation of bupropion.

268 ZYBAN is contraindicated in patients undergoing abrupt discontinuation of alcohol or  
269 sedatives (including benzodiazepines).

270 The concurrent administration of ZYBAN and a monoamine oxidase (MAO) inhibitor is  
271 contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and  
272 initiation of treatment with ZYBAN.

273 ZYBAN is contraindicated in patients who have shown an allergic response to bupropion or  
274 the other ingredients that make up ZYBAN.

## 275 **WARNINGS**

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

290 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
291 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24  
292 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of  
293 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of  
294 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000  
295 patients. There was considerable variation in risk of suicidality among drugs, but a tendency  
296 toward an increase in the younger patients for almost all drugs studied. There were differences in  
297 absolute risk of suicidality across the different indications, with the highest incidence in MDD.  
298 The risk differences (drug vs placebo), however, were relatively stable within age strata and  
299 across indications. These risk differences (drug-placebo difference in the number of cases of  
300 suicidality per 1,000 patients treated) are provided in Table 4.

301

302 **Table 4**

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

303

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

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

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

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

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

325 **Families and caregivers of patients being treated with antidepressants for major**  
326 **depressive disorder or other indications, both psychiatric and nonpsychiatric, should be**  
327 **alerted about the need to monitor patients for the emergence of agitation, irritability,**  
328 **unusual changes in behavior, and the other symptoms described above, as well as the**  
329 **emergence of suicidality, and to report such symptoms immediately to health care**  
330 **providers. Such monitoring should include daily observation by families and caregivers.**  
331 Prescriptions for ZYBAN should be written for the smallest quantity of tablets consistent with  
332 good patient management, in order to reduce the risk of overdose.

333 **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial  
334 presentation of bipolar disorder. It is generally believed (though not established in controlled  
335 trials) that treating such an episode with an antidepressant alone may increase the likelihood of  
336 precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the  
337 symptoms described above represent such a conversion is unknown. However, prior to initiating  
338 treatment with an antidepressant, patients with depressive symptoms should be adequately  
339 screened to determine if they are at risk for bipolar disorder; such screening should include a  
340 detailed psychiatric history, including a family history of suicide, bipolar disorder, and  
341 depression. It should be noted that ZYBAN is not approved for use in treating bipolar  
342 depression.

343 **Patients should be made aware that ZYBAN contains the same active ingredient found**  
344 **in WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL used to treat depression,**  
345 **and that ZYBAN should not be used in combination with WELLBUTRIN (bupropion**  
346 **hydrochloride), the immediate release formulation; WELLBUTRIN SR (bupropion**  
347 **hydrochloride), the sustained-release formulation; WELLBUTRIN XL (bupropion**  
348 **hydrochloride), the extended-release formulation; or any other medications that contain**  
349 **bupropion.**

350

351 **Seizures:** Because the use of bupropion is associated with a dose-dependent risk of  
352 seizures, *clinicians should not prescribe doses over 300 mg/day for smoking cessation.* The  
353 risk of seizures is also related to patient factors, clinical situation, and concomitant  
354 medications, which must be considered in selection of patients for therapy with ZYBAN.  
355 ZYBAN should be discontinued and not restarted in patients who experience a seizure  
356 while on treatment.

357 • **Dose:** *For smoking cessation, doses above 300 mg/day should not be used.* The seizure  
358 rate associated with doses of sustained-release bupropion up to 300 mg/day is  
359 approximately 0.1% (1/1,000). This incidence was prospectively determined during an  
360 8-week treatment exposure in approximately 3,100 depressed patients.

361 **Data for the immediate-release formulation of bupropion revealed a seizure incidence**  
362 **of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300**  
363 **to 450 mg/day. In addition, the estimated seizure incidence increases almost tenfold**  
364 **between 450 and 600 mg/day.**

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

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

- 373 • **Concomitant medications:** Many medications (e.g., antipsychotics, antidepressants,  
374 theophylline, systemic steroids) are known to lower seizure threshold.  
375 **Recommendations for Reducing the Risk of Seizure:** Retrospective analysis of  
376 clinical experience gained during the development of bupropion suggests that the risk of  
377 seizure may be minimized if
- 378 • the total daily dose of ZYBAN does *not* exceed 300 mg (the maximum recommended  
379 dose for smoking cessation), and
  - 380 • the recommended daily dose for most patients (300 mg/day) is administered in divided  
381 doses (150 mg twice daily).
  - 382 • No single dose should exceed 150 mg to avoid high peak concentrations of bupropion  
383 and/or its metabolites.

384 ZYBAN should be administered with extreme caution to patients with a history of  
385 seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with  
386 other agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that  
387 lower seizure threshold.

388 **Hepatic Impairment:** ZYBAN should be used with extreme caution in patients with severe  
389 hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak  
390 bupropion levels are substantially increased and accumulation is likely to occur in such  
391 patients to a greater extent than usual. The dose should not exceed 150 mg every other day  
392 in these patients (see CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE  
393 AND ADMINISTRATION).

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

## 398 PRECAUTIONS

399 **General: Allergic Reactions:** Anaphylactoid/anaphylactic reactions characterized by  
400 symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have  
401 been reported at a rate of about 1 to 3 per thousand in clinical trials of ZYBAN. In addition, there  
402 have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson  
403 syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking  
404 ZYBAN and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions  
405 (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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

409 **Insomnia:** In the dose-response smoking cessation trial, 29% of patients treated with  
410 150 mg/day of ZYBAN and 35% of patients treated with 300 mg/day of ZYBAN experienced  
411 insomnia, compared to 21% of placebo-treated patients. Symptoms were sufficiently severe to

412 require discontinuation of treatment in 0.6% of patients treated with ZYBAN and none of the  
413 patients treated with placebo.

414 In the comparative trial, 40% of the patients treated with 300 mg/day of ZYBAN, 28% of the  
415 patients treated with 21 mg/day of NTS, and 45% of the patients treated with the combination of  
416 ZYBAN and NTS experienced insomnia compared to 18% of placebo-treated patients.

417 Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients  
418 treated with ZYBAN and none of the patients in the other 3 treatment groups.

419 Insomnia may be minimized by avoiding bedtime doses and, if necessary, reduction in dose.

420 **Psychosis, Confusion, and Other Neuropsychiatric Phenomena:** In clinical trials  
421 with ZYBAN conducted in nondepressed smokers, the incidence of neuropsychiatric side effects  
422 was generally comparable to placebo. Depressed patients treated with bupropion in depression  
423 trials have been reported to show a variety of neuropsychiatric signs and symptoms including  
424 delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some  
425 cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

426 **Activation of Psychosis and/or Mania:** Antidepressants can precipitate manic episodes  
427 in bipolar disorder patients during the depressed phase of their illness and may activate latent  
428 psychosis in other susceptible individuals. The sustained-release formulation of bupropion is  
429 expected to pose similar risks. There were no reports of activation of psychosis or mania in  
430 clinical trials with ZYBAN conducted in nondepressed smokers.

431 **Depression and Nicotine Withdrawal:** Depressed mood may be a symptom of nicotine  
432 withdrawal. Depression, rarely including suicidal ideation, has been reported in patients  
433 undergoing a smoking cessation attempt (see **WARNINGS: Clinical Worsening and Suicide  
434 Risk**).

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

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

450 There is no clinical experience establishing the safety of ZYBAN in patients with a recent  
451 history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if

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

458 **Hepatic Impairment:** ZYBAN should be used with extreme caution in patients with severe  
459 hepatic cirrhosis. In these patients, a reduced frequency of dosing is required. ZYBAN should be  
460 used with caution in patients with hepatic impairment (including mild to moderate hepatic  
461 cirrhosis) and reduced frequency of dosing should be considered in patients with mild to  
462 moderate hepatic cirrhosis.

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

466 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
467 patients with renal impairment. An inter-study comparison between normal subjects and patients  
468 with end-stage renal failure demonstrated that the parent drug  $C_{max}$  and AUC values were  
469 comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
470 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage  
471 renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are  
472 further metabolized and subsequently excreted by the kidneys. ZYBAN should be used with  
473 caution in patients with renal impairment and a reduced frequency of dosing should be  
474 considered as bupropion and the metabolites of bupropion may accumulate in such patients to a  
475 greater extent than usual. The patient should be closely monitored for possible adverse effects  
476 that could indicate high drug or metabolite levels.

477 **Information for Patients:** Although ZYBAN is not indicated for treatment of depression, it  
478 contains the same active ingredient as the antidepressant medications WELLBUTRIN,  
479 WELLBUTRIN SR, and WELLBUTRIN XL. Prescribers or other health professionals should  
480 inform patients, their families, and their caregivers about the benefits and risks associated with  
481 treatment with ZYBAN and should counsel them in its appropriate use. A patient Medication  
482 Guide about “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and  
483 Suicidal Thoughts or Actions” and other important information about using ZYBAN is available  
484 for ZYBAN. The prescriber or health professional should instruct patients, their families, and  
485 their caregivers to read the Medication Guide and should assist them in understanding its  
486 contents. Patients should be given the opportunity to discuss the contents of the Medication  
487 Guide and to obtain answers to any questions they may have. The complete text of the  
488 Medication Guide is reprinted at the end of this document.

489 Patients should be advised of the following issues and asked to alert their prescriber if these  
490 occur while taking ZYBAN.

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

502 Patients should be made aware that ZYBAN contains the same active ingredient found in  
503 WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL used to treat depression and that  
504 ZYBAN should not be used in conjunction with WELLBUTRIN, the immediate-release  
505 formulation; WELLBUTRIN SR, the sustained-release formulation; WELLBUTRIN XL, the  
506 extended-release formulation; or any other medications that contain bupropion hydrochloride.

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

508 **Drug Interactions:** In vitro studies indicate that bupropion is primarily metabolized to  
509 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug  
510 interaction between ZYBAN and drugs that are substrates or inhibitors of the CYP2B6  
511 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies  
512 suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
513 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
514 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
515 appear to be produced by the cytochrome P450 isoenzymes. Few systemic data have been  
516 collected on the metabolism of ZYBAN following concomitant administration with other drugs  
517 or, alternatively, the effect of concomitant administration of ZYBAN on the metabolism of other  
518 drugs.

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

521 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
522 humans. However, following chronic administration of bupropion, 100 mg t.i.d to 8 healthy male  
523 volunteers for 14 days, there was no evidence of induction of its own metabolism. Because  
524 bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical  
525 activity. In particular, certain drugs may induce the metabolism of bupropion (e.g.,  
526 carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of  
527 bupropion (e.g., cimetidine). The effects of concomitant administration of cimetidine on the  
528 pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male  
529 volunteers. Following oral administration of two 150-mg ZYBAN tablets with and without  
530 800 mg of cimetidine, the pharmacokinetics of bupropion and its hydroxy metabolite were

531 unaffected. However, there were 16% and 32% increases, respectively, in the AUC and  $C_{max}$  of  
532 the combined moieties of threo- and erythro- bupropion.

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

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

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

554 **Levodopa and Amantadine:** Limited clinical data suggest a higher incidence of adverse  
555 experiences in patients receiving bupropion concurrently with either levodopa or amantadine.  
556 Administration of ZYBAN to patients receiving either levodopa or amantadine concurrently  
557 should be undertaken with caution, using small initial doses and gradual dose increases.

558 **Drugs that Lower Seizure Threshold:** Concurrent administration of ZYBAN and agents  
559 (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) that lower seizure  
560 threshold should be undertaken only with extreme caution (see WARNINGS).

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

562 **Smoking Cessation:** Physiological changes resulting from smoking cessation itself, with  
563 or without treatment with ZYBAN, may alter the pharmacokinetics of some concomitant  
564 medications, which may require dosage adjustment. Blood concentrations of concomitant  
565 medications that are extensively metabolized, such as theophylline and warfarin, may be  
566 expected to increase following smoking cessation due to de-induction of hepatic enzymes.

567 **Alcohol:** In post-marketing experience, there have been rare reports of adverse  
568 neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol  
569 during treatment with ZYBAN. The consumption of alcohol during treatment with ZYBAN  
570 should be minimized or avoided (also see CONTRAINDICATIONS).

571 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lifetime carcinogenicity studies  
572 were performed in rats and mice at doses up to 300 and 150 mg/kg per day, respectively. These  
573 doses are approximately 10 and 2 times the maximum recommended human dose (MRHD),  
574 respectively, on a mg/m<sup>2</sup> basis. In the rat study, there was an increase in nodular proliferative  
575 lesions of the liver at doses of 100 to 300 mg/kg per day (approximately 3 to 10 times the  
576 MRHD on a mg/m<sup>2</sup> basis); lower doses were not tested. The question of whether or not such  
577 lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions  
578 were not seen in the mouse study, and no increase in malignant tumors of the liver and other  
579 organs was seen in either study.

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

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

584 **Pregnancy: Teratogenic Effects:** Pregnancy Category C. In studies conducted in rats and  
585 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively  
586 (approximately 14 and 10 times the maximum recommended human dose [MRHD], respectively,  
587 on a mg/m<sup>2</sup> basis), during the period of organogenesis. No clear evidence of teratogenic activity  
588 was found in either species; however, in rabbits, slightly increased incidences of fetal  
589 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,  
590 approximately 2 times the MRHD on a mg/m<sup>2</sup> basis) and greater. Decreased fetal weights were  
591 seen at 50 mg/kg and greater.

592 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
593 10 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
594 there were no apparent adverse effects on offspring development.

595 One study has been conducted in pregnant women. This retrospective, managed-care database  
596 study assessed the risk of congenital malformations overall, and cardiovascular malformations  
597 specifically, following exposure to bupropion in the first trimester compared to the risk of these  
598 malformations following exposure to other antidepressants in the first trimester and bupropion  
599 outside of the first trimester. This study included 7,005 infants with antidepressant exposure  
600 during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study  
601 showed no greater risk for congenital malformations overall, or cardiovascular malformations  
602 specifically, following first trimester bupropion exposure compared to exposure to all other  
603 antidepressants in the first trimester, or bupropion outside of the first trimester. The results of  
604 this study have not been corroborated. ZYBAN should be used during pregnancy only if the  
605 potential benefit justifies the potential risk to the fetus. Pregnant smokers should be encouraged  
606 to attempt cessation using educational and behavioral interventions before pharmacological  
607 approaches are used.

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

611 **Labor and Delivery:** The effect of ZYBAN on labor and delivery in humans is unknown.

612 **Nursing Mothers:** Bupropion and its metabolites are secreted in human milk. Because of the  
613 potential for serious adverse reactions in nursing infants from ZYBAN, a decision should be  
614 made whether to discontinue nursing or to discontinue the drug, taking into account the  
615 importance of the drug to the mother.

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

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

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

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

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

638 The information included under ADVERSE REACTIONS is based primarily on data from the  
639 dose-response trial and the comparative trial that evaluated ZYBAN for smoking cessation (see  
640 CLINICAL TRIALS). Information on additional adverse events associated with the  
641 sustained-release formulation of bupropion in depression trials, as well as the immediate-release  
642 formulation of bupropion, is included in a separate section (see Other Events Observed During  
643 the Clinical Development and Postmarketing Experience of Bupropion).

644 **Adverse Events Associated With the Discontinuation of Treatment:** Adverse events  
645 were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 patients  
646 treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events  
647 leading to discontinuation of treatment with ZYBAN included nervous system disturbances  
648 (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

649 **Incidence of Commonly Observed Adverse Events:** The most commonly observed  
650 adverse events consistently associated with the use of ZYBAN were dry mouth and insomnia.  
651 The most commonly observed adverse events were defined as those that consistently occurred at  
652 a rate of 5 percentage points greater than that for placebo across clinical studies.

653 **Dose Dependency of Adverse Events:** The incidence of dry mouth and insomnia may be  
654 related to the dose of ZYBAN. The occurrence of these adverse events may be minimized by  
655 reducing the dose of ZYBAN. In addition, insomnia may be minimized by avoiding bedtime  
656 doses.

657 **Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated**  
658 **With ZYBAN:** Table 5 enumerates selected treatment-emergent adverse events from the  
659 dose-response trial that occurred at an incidence of 1% or more and were more common in  
660 patients treated with ZYBAN compared to those treated with placebo. Table 6 enumerates  
661 selected treatment-emergent adverse events from the comparative trial that occurred at an  
662 incidence of 1% or more and were more common in patients treated with ZYBAN, NTS, or the  
663 combination of ZYBAN and NTS compared to those treated with placebo. Reported adverse  
664 events were classified using a COSTART-based dictionary.

665  
666 **Table 5. Treatment-Emergent Adverse Event Incidence in the Dose-Response Trial\***

Body System/ Adverse Experience	ZYBAN 100 to 300 mg/day (n = 461) %	Placebo (n = 150) %
Body (General)		
Neck pain	2	<1
Allergic reaction	1	0
Cardiovascular		
Hot flashes	1	0
Hypertension	1	<1
Digestive		
Dry mouth	11	5
Increased appetite	2	<1
Anorexia	1	<1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous system		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1

Thinking abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	<1
Rash	3	<1
Dry skin	2	0
Urticaria	1	0
Special senses		
Taste perversion	2	<1

667 \* Selected adverse events with an incidence of at least 1% of patients treated with ZYBAN  
668 and more frequent than in the placebo group.  
669  
670

**Table 6. Treatment-Emergent Adverse Event Incidence in the Comparative Trial\***

Adverse Experience (COSTART Term)	ZYBAN 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
Digestive				
Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2

Nervous system				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction <sup>†</sup>	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0
Special Senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	<1	0

671 \* Selected adverse events with an incidence of at least 1% of patients treated with either ZYBAN,  
672 NTS, or the combination of ZYBAN and NTS and more frequent than in the placebo group.

673 <sup>†</sup> Patients randomized to ZYBAN or placebo received placebo patches.

674

675 ZYBAN was well-tolerated in the long-term maintenance trial that evaluated chronic  
676 administration of ZYBAN for up to 1 year and in the COPD trial that evaluated patients with  
677 mild-to-moderate COPD for a 12-week period. Adverse events in both studies were  
678 quantitatively and qualitatively similar to those observed in the dose-response and comparative  
679 trials.

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

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

686 Adverse events for which frequencies are provided below occurred in clinical trials with  
687 bupropion sustained-release. The frequencies represent the proportion of patients who  
688 experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled  
689 studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced  
690 an adverse event requiring discontinuation of treatment in an open-label surveillance study with  
691 bupropion sustained-release tablets (n = 3,100). All treatment-emergent adverse events are  
692 included except those listed in Tables 5 and 6, those events listed in other safety-related sections  
693 of the insert, those adverse events subsumed under COSTART terms that are either overly  
694 general or excessively specified so as to be uninformative, those events not reasonably associated  
695 with the use of the drug, and those events that were not serious and occurred in fewer than  
696 2 patients.

697 Events are further categorized by body system and listed in order of decreasing frequency  
698 according to the following definitions of frequency: Frequent adverse events are defined as those  
699 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
700 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

701 Adverse events for which frequencies are not provided occurred in clinical trials or  
702 postmarketing experience with bupropion. Only those adverse events not previously listed for  
703 sustained-release bupropion are included. The extent to which these events may be associated  
704 with ZYBAN is unknown.

705 **Body (General):** Frequent were asthenia, fever, and headache. Infrequent were back pain,  
706 chills, inguinal hernia, musculoskeletal chest pain, pain, and photosensitivity. Rare was malaise.  
707 Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of  
708 delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS).

709 **Cardiovascular:** Infrequent were flushing, migraine, postural hypotension, stroke,  
710 tachycardia, and vasodilation. Rare was syncope. Also observed were cardiovascular disorder,  
711 complete AV block, extrasystoles, hypotension, hypertension (in some cases severe, see  
712 PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

713 **Digestive:** Frequent were dyspepsia, flatulence, and vomiting. Infrequent were abnormal  
714 liver function, bruxism, dysphagia, gastric reflux, gingivitis, glossitis, jaundice, and stomatitis.  
715 Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage,  
716 gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage,  
717 pancreatitis, stomach ulcer, and stool abnormality.

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

720 **Hemic and Lymphatic:** Infrequent was ecchymosis. Also observed were anemia,  
721 leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT  
722 and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were  
723 observed when bupropion was co-administered with warfarin.

724 **Metabolic and Nutritional:** Infrequent were edema, increased weight, and peripheral  
725 edema. Also observed was glycosuria.

726 **Musculoskeletal:** Infrequent were leg cramps and twitching. Also observed were arthritis  
727 and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

728 **Nervous System:** Frequent were agitation, depression, and irritability. Infrequent were  
729 abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory,  
730 depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,  
731 paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and  
732 hypomania. Also observed were abnormal electroencephalogram (EEG), aggression, akinesia,  
733 aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal  
734 syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy,  
735 paranoid ideation, restlessness, and unmasking tardive dyskinesia.

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

737 **Skin:** Frequent was sweating. Infrequent was acne and dry skin. Rare was maculopapular  
738 rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

739 **Special Senses:** Frequent was blurred vision or diplopia. Infrequent were accommodation  
740 abnormality and dry eye. Also observed were deafness, increased intraocular pressure, and  
741 mydriasis.

742 **Urogenital:** Frequent was urinary frequency. Infrequent were impotence, polyuria, and  
743 urinary urgency. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria,  
744 gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence,  
745 urinary retention, urinary tract disorder, and vaginitis.

## 746 **DRUG ABUSE AND DEPENDENCE**

747 ZYBAN is likely to have a low abuse potential.

748 **Humans:** There have been few reported cases of drug dependence and withdrawal symptoms  
749 associated with the immediate-release formulation of bupropion. In human studies of abuse  
750 liability, individuals experienced with drugs of abuse reported that bupropion produced a feeling  
751 of euphoria and desirability. In these subjects, a single dose of 400 mg (1.33 times the  
752 recommended daily dose) of bupropion produced mild amphetamine-like effects compared to  
753 placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories  
754 (ARCI), which is indicative of euphorigenic properties and a score intermediate between placebo  
755 and amphetamine on the Liking Scale of the ARCI.

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

764 The possibility that bupropion may induce dependence should be kept in mind when  
765 evaluating the desirability of including the drug in smoking cessation programs of individual  
766 patients.

## 767 **OVERDOSAGE**

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

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

778 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
779 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
780 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
781 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
782 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
783 symptomatic patients.

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

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

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

## 795 **DOSAGE AND ADMINISTRATION**

796 **Usual Dosage for Adults:** The recommended and maximum dose of ZYBAN is 300 mg/day,  
797 given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first  
798 3 days, followed by a dose increase for most patients to the recommended usual dose of  
799 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses  
800 above 300 mg/day should not be used (see WARNINGS). ZYBAN should be swallowed whole  
801 and not crushed, divided, or chewed. Treatment with ZYBAN should be initiated **while the**  
802 **patient is still smoking**, since approximately 1 week of treatment is required to achieve

803 steady-state blood levels of bupropion. Patients should set a “target quit date” within the first  
804 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN  
805 should be continued for 7 to 12 weeks; longer treatment should be guided by the relative benefits  
806 and risks for individual patients. If a patient has not made significant progress towards  
807 abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit  
808 during that attempt, and treatment should probably be discontinued. Conversely, a patient who  
809 successfully quits after 7 to 12 weeks of treatment should be considered for ongoing therapy with  
810 ZYBAN. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important  
811 that patients continue to receive counseling and support throughout treatment with ZYBAN, and  
812 for a period of time thereafter.

813 **Individualization of Therapy:** Patients are more likely to quit smoking and remain abstinent  
814 if they are seen frequently and receive support from their physicians or other health care  
815 professionals. It is important to ensure that patients read the instructions provided to them and  
816 have their questions answered. Physicians should review the patient’s overall smoking cessation  
817 program that includes treatment with ZYBAN. Patients should be advised of the importance of  
818 participating in the behavioral interventions, counseling, and/or support services to be used in  
819 conjunction with ZYBAN. See information for patients at the end of the package insert.

820 The goal of therapy with ZYBAN is complete abstinence. If a patient has not made significant  
821 progress towards abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he  
822 or she will quit during that attempt, and treatment should probably be discontinued.

823 Patients who fail to quit smoking during an attempt may benefit from interventions to improve  
824 their chances for success on subsequent attempts. Patients who are unsuccessful should be  
825 evaluated to determine why they failed. A new quit attempt should be encouraged when factors  
826 that contributed to failure can be eliminated or reduced, and conditions are more favorable.

827 **Maintenance:** Nicotine dependence is a chronic condition. Some patients may need  
828 continuous treatment. Systematic evaluation of ZYBAN 300 mg/day for maintenance therapy  
829 demonstrated that treatment for up to 6 months was efficacious. Whether to continue treatment  
830 with ZYBAN for periods longer than 12 weeks for smoking cessation must be determined for  
831 individual patients.

832 **Combination Treatment With ZYBAN and a Nicotine Transdermal System (NTS):**  
833 Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation. The  
834 prescriber should review the complete prescribing information for both ZYBAN and NTS before  
835 using combination treatment. See also CLINICAL TRIALS for methods and dosing used in the  
836 ZYBAN and NTS combination trial. Monitoring for treatment-emergent hypertension in patients  
837 treated with the combination of ZYBAN and NTS is recommended.

838 **Dosage Adjustment for Patients with Impaired Hepatic Function:** ZYBAN should be  
839 used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed  
840 150 mg every other day in these patients. ZYBAN should be used with caution in patients with  
841 hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency of

842 dosing should be considered in patients with mild to moderate hepatic cirrhosis (see CLINICAL  
843 PHARMACOLOGY, WARNINGS, and PRECAUTIONS).

844 **Dosage Adjustment for Patients with Impaired Renal Function:** ZYBAN should be  
845 used with caution in patients with renal impairment and a reduced frequency of dosing should be  
846 considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

## 847 **HOW SUPPLIED**

848 ZYBAN Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round,  
849 biconvex, film-coated tablets printed with “ZYBAN 150” in bottles of 60 (NDC 0173-0556-02)  
850 tablets and the ZYBAN Advantage Pack<sup>®</sup> containing 1 bottle of 60 (NDC 0173-0556-01) tablets.

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

853

## 854 **MEDICATION GUIDE**

855 **ZYBAN<sup>®</sup> (zi ban)**

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

857

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

862

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

866

867 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and**  
868 **Suicidal Thoughts or Actions**

869

870 Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the  
871 antidepressant medications WELLBUTRIN<sup>®</sup>, WELLBUTRIN SR<sup>®</sup>, and WELLBUTRIN XL<sup>®</sup>.

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

874 **about:**

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

877

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

- 880 **1. Antidepressant medicines may increase suicidal thoughts or actions in some children,**  
881 **teenagers, and young adults within the first few months of treatment.**
- 882 **2. Depression and other serious mental illnesses are the most important causes of suicidal**  
883 **thoughts and actions. Some people may have a particularly high risk of having suicidal**  
884 **thoughts or actions.** These include people who have (or have a family history of) bipolar  
885 illness (also called manic-depressive illness) or suicidal thoughts or actions.
- 886 **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a**  
887 **family member?**
- 888 • Pay close attention to any changes, especially sudden changes, in mood, behaviors,  
889 thoughts, or feelings. This is very important when an antidepressant medicine is started or  
890 when the dose is changed.
  - 891 • Call the healthcare provider right away to report new or sudden changes in mood,  
892 behavior, thoughts, or feelings.
  - 893 • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare  
894 provider between visits as needed, especially if you have concerns about symptoms.
- 895

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

- 898
- thoughts about suicide or dying
  - attempts to commit suicide
  - new or worse depression
  - new or worse anxiety
  - feeling very agitated or restless
  - panic attacks
  - trouble sleeping (insomnia)
  - new or worse irritability
  - acting aggressive, being angry, or violent
  - acting on dangerous impulses
  - an extreme increase in activity and talking (mania)
  - other unusual changes in behavior or mood

899

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

- 901 • **Never stop an antidepressant medicine without first talking to a healthcare provider.**  
902 Stopping an antidepressant medicine suddenly can cause other symptoms.
- 903 • **Antidepressants are medicines used to treat depression and other illnesses.** It is  
904 important to discuss all the risks of treating depression and also the risks of not treating it.  
905 Patients and their families or other caregivers should discuss all treatment choices with the  
906 healthcare provider, not just the use of antidepressants.
- 907 • **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the  
908 side effects of the medicine prescribed for you or your family member.
- 909 • **Antidepressant medicines can interact with other medicines.** Know all of the medicines  
910 that you or your family member takes. Keep a list of all medicines to show the healthcare  
911 provider. Do not start new medicines without first checking with your healthcare provider.

- 912 • **Not all antidepressant medicines prescribed for children are FDA approved for use in**  
913 **children.** Talk to your child’s healthcare provider for more information.

914

915 ZYBAN has not been studied in children under the age of 18 and is not approved for use in  
916 children and teenagers.

917

### 918 **What other important information should I know about ZYBAN?**

919

920 **There is a chance of having a seizure (convulsion, fit) with ZYBAN, especially in people:**

- 921 • with certain medical problems.  
922 • who take certain medicines.

923

924 The chance of having seizures increases with higher doses of ZYBAN. For more information,  
925 see the sections “Who should not take ZYBAN?” and “What should I tell my doctor before using  
926 ZYBAN?” Tell your doctor about all of your medical conditions and all the medicines you take.

927 **Do not take any other medicines while you are using ZYBAN unless your doctor has said it**  
928 **is okay to take them.**

929

930 **If you have a seizure while taking ZYBAN, stop taking the tablets and call your doctor**  
931 **right away.** Do not take ZYBAN again if you have a seizure.

932

### 933 **What is ZYBAN?**

934 ZYBAN is a prescription medicine to help people quit smoking. Studies have shown that more  
935 than one third of people quit smoking for at least 1 month while taking ZYBAN and participating  
936 in a patient support program. For many patients, ZYBAN reduces withdrawal symptoms and the  
937 urge to smoke. ZYBAN should be used with a patient support program. It is important to  
938 participate in the behavioral program, counseling, or other support program your health care  
939 professional recommends.

940

### 941 **Who should not take ZYBAN?**

942 **Do not take ZYBAN if you:**

- 943 • have or had a seizure disorder or epilepsy.  
944 • **are taking WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, or any other**  
945 **medicines that contain bupropion hydrochloride.** Bupropion is the same active ingredient  
946 that is in ZYBAN.  
947 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
948 make you sleepy) or benzodiazepines and you stop using them all of a sudden.  
949 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
950 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
951 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).  
952 • have or had an eating disorder such as anorexia nervosa or bulimia.

- 953 • are allergic to the active ingredient in ZYBAN, bupropion, or to any of the inactive  
954 ingredients. See the end of this leaflet for a complete list of ingredients in ZYBAN.

955

956 **Can I take ZYBAN if I have mild-to-moderate chronic bronchitis and/or emphysema (also**  
957 **called chronic obstructive pulmonary disease or COPD)?**

958 Yes, ZYBAN combined with a behavior modification program has been shown to help people  
959 with COPD quit smoking. It is important to participate in the behavior program, counseling, or  
960 other support program your health care professional recommends.

961

962 **What should I tell my doctor before using ZYBAN?**

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

983

984 **How should I take ZYBAN?**

- 985 • Take ZYBAN exactly as prescribed by your doctor.
- 986 • **Do not chew, cut, or crush ZYBAN Tablets.** You must swallow the tablets whole. **Tell**  
987 **your doctor if you cannot swallow medicine tablets.**
- 988 • Take ZYBAN at the same time each day.
- 989 • Take your doses of ZYBAN at least 8 hours apart.
- 990 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and  
991 take your next tablet at the regular time. **This is very important.** Too much ZYBAN can  
992 increase your chance of having a seizure.

- 993 • If you take too much ZYBAN, or overdose, call your local emergency room or poison  
994 control center right away.  
995 • **Do not take any other medicines while using ZYBAN unless your doctor has told you it**  
996 **is okay.**  
997 • Do not change your dose or stop taking ZYBAN without talking with your doctor first.  
998

999 **How long should I take ZYBAN?**

1000 Most people should take ZYBAN for at least 7 to 12 weeks. Some people may need to take  
1001 ZYBAN for a longer period of time to assist in their smoking cessation efforts. Follow your  
1002 doctor's instructions.

1003

1004 **When should I stop smoking?**

1005 It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to  
1006 maximize your chance of quitting, you should not stop smoking until you have been taking  
1007 ZYBAN for 1 week. You should set a date to stop smoking during the second week you're  
1008 taking ZYBAN.

1009

1010 **Can I smoke while taking ZYBAN?**

1011 It is not physically dangerous to smoke and use ZYBAN at the same time. However, continuing  
1012 to smoke after the date you set to stop smoking will seriously reduce your chance of breaking  
1013 your smoking habit.

1014

1015 **Can ZYBAN be used at the same time as nicotine patches?**

1016 Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together  
1017 under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise  
1018 your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine  
1019 replacement therapy because your doctor will probably want to check your blood pressure  
1020 regularly to make sure that it stays within acceptable levels.

1021

1022 **DO NOT SMOKE AT ANY TIME** if you are using a nicotine patch or any other nicotine  
1023 product along with ZYBAN. It is possible to get too much nicotine and have serious side effects.

1024

1025 **What should I avoid while taking ZYBAN?**

- 1026 • Do not drink a lot of alcohol while taking ZYBAN. If you usually drink a lot of alcohol, talk  
1027 with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may  
1028 increase your chance of having seizures.  
1029 • Do not drive a car or use heavy machinery until you know how ZYBAN affects you.  
1030 ZYBAN can impair your ability to perform these tasks.

1031

1032 **What are possible side effects of ZYBAN?**

- 1033 • **Seizures.** Some patients get seizures while taking ZYBAN. **If you have a seizure while**  
1034 **taking ZYBAN, stop taking the tablets and call your doctor right away.** Do not take  
1035 ZYBAN again if you have a seizure.
- 1036 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
1037 severe, while taking ZYBAN. The chance of high blood pressure may be increased if you  
1038 also use nicotine replacement therapy (for example, a nicotine patch) to help you stop  
1039 smoking (see “Can ZYBAN be used at the same time as nicotine patches?”).
- 1040 • **Severe allergic reactions: Stop taking ZYBAN and call your doctor right away** if you get  
1041 a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the  
1042 eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be  
1043 signs of a serious allergic reaction.
- 1044 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1045 taking ZYBAN, including delusions (believe you are someone else), hallucinations (seeing or  
1046 hearing things that are not there), paranoia (feeling that people are against you), or feeling  
1047 confused. If this happens to you, call your doctor.

1048

1049 The most common side effects of ZYBAN are dry mouth and difficulty sleeping. These side  
1050 effects are generally mild and often disappear after a few weeks. If you have difficulty sleeping,  
1051 do not take your medicine too close to bedtime.

1052

1053 Tell your doctor right away about any side effects that bother you.

1054

1055 These are not all the side effects of ZYBAN. For a complete list, ask your doctor or pharmacist.

1056

#### 1057 **How should I store ZYBAN?**

- 1058 • Store ZYBAN at room temperature. Store out of direct sunlight. Keep ZYBAN in its tightly  
1059 closed bottle.
- 1060 • ZYBAN may have an odor.

1061

#### 1062 **General Information about ZYBAN.**

- 1063 • Medicines are sometimes prescribed for purposes other than those listed in a Medication  
1064 Guide. Do not use ZYBAN for a condition for which it was not prescribed. Do not give  
1065 ZYBAN to other people, even if they have the same symptoms you have. It may harm them.  
1066 Keep ZYBAN out of the reach of children.

1067

1068 This Medication Guide summarizes important information about ZYBAN. For more information,  
1069 talk with your doctor. You can ask your doctor or pharmacist for information about ZYBAN that  
1070 is written for health professionals.

1071

#### 1072 **What are the ingredients in ZYBAN?**

1073 Active ingredient: bupropion hydrochloride.

1074

1075 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1076 microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. The tablets  
1077 are printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake  
1078 and FD&C Red No. 40 Lake.

1079

1080 \*The following are registered trademarks of their respective manufacturers: NARDIL<sup>®</sup>/Warner  
1081 Lambert Company; MARPLAN<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

1082

1083 **R<sub>x</sub> only**

1084

1085 This Medication Guide has been approved by the U.S. Food and Drug Administration.

1086

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1088



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1101

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