



NDA 20-711/S-027

GlaxoSmithKline  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709

Attention: Mary E. Martinson  
Director, Psychiatry US Regulatory Affairs

Dear Ms. Martinson:

Please refer to your supplemental new drug application dated May 16, 2006, received May 17, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zyban® (bupropion hydrochloride) Sustained-Release Tablets.

This “Changes Being Effected” supplemental new drug application provides for revisions to the **PRECAUTIONS – Pregnancy** section to change the pregnancy category from Pregnancy Category B to Pregnancy Category C.

We have completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on June 28, 2006, and attached to this letter (enclosure).

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
WO 22, Room 4447  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dominic Chiapperino, Regulatory Project Manager, at (301) 796-1183.

Sincerely,

*{See appended electronic signature page}*

Bob Rappaport, M.D.  
Director  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

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

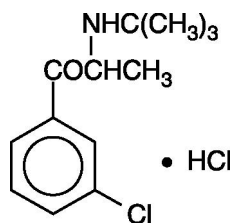
**Suicidality in Children and Adolescents**

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 of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of ZYBAN or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ZYBAN is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

**DESCRIPTION**

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:



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

47 **CLINICAL PHARMACOLOGY**

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

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

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

61 Following oral administration of ZYBAN to healthy volunteers, peak plasma concentrations  
62 of bupropion are achieved within 3 hours. The mean peak concentration ( $C_{max}$ ) values were  
63 91 and 143 ng/mL from 2 single-dose (150-mg) studies. At steady state, the mean  $C_{max}$  following  
64 a 150-mg dose every 12 hours is 136 ng/mL.

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

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

73 distribution ( $V_{ss}/F$ ) estimated from a single 150-mg dose given to 17 subjects is 1,950 L  
74 (20% CV).

75 **Metabolism:** Bupropion is extensively metabolized in humans. Three metabolites have been  
76 shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group  
77 of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion,  
78 which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome  
79 P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion,  
80 while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion.  
81 Oxidation of the bupropion side chain results in the formation of a glycine conjugate of  
82 meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency  
83 and toxicity of the metabolites relative to bupropion have not been fully characterized. However,  
84 it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is  
85 one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are  
86 5-fold less potent than bupropion. This may be of clinical importance because the plasma  
87 concentrations of the metabolites are as high or higher than those of bupropion.

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

93 Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur  
94 approximately 6 hours after administration of ZYBAN Tablets. Peak plasma concentrations of  
95 hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state.  
96 The elimination half-life of hydroxybupropion is approximately 20 ( $\pm 5$ ) hours, and its AUC at  
97 steady state is about 17 times that of bupropion. The times to peak concentrations for the  
98 erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the  
99 hydroxybupropion metabolite; however, their elimination half-lives are longer, 33 ( $\pm 10$ ) and  
100 37 ( $\pm 13$ ) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,  
101 respectively.

102 Bupropion and its metabolites exhibit linear kinetics following chronic administration of  
103 300 to 450 mg/day.

104 **Elimination:** The mean ( $\pm\%$  CV) apparent clearance (Cl/F) estimated from 2 single-dose  
105 (150-mg) studies are 135 ( $\pm 20\%$ ) and 209 L/hr ( $\pm 21\%$ ). Following chronic dosing of 150 mg of  
106 ZYBAN every 12 hours for 14 days ( $n = 34$ ), the mean Cl/F at steady state was 160 L/hr ( $\pm 23\%$ ).  
107 The mean elimination half-life of bupropion estimated from a series of studies is approximately  
108 21 hours. Estimates of the half-lives of the metabolites determined from a multiple-dose study  
109 were 20 hours ( $\pm 25\%$ ) for hydroxybupropion, 37 hours ( $\pm 35\%$ ) for threohydrobupropion, and  
110 33 hours ( $\pm 30\%$ ) for erythrohydrobupropion. Steady-state plasma concentrations of bupropion  
111 and metabolites are reached within 5 and 8 days, respectively.

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

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

120 In a study comparing the treatment combination of ZYBAN and nicotine transdermal system  
121 (NTS) versus ZYBAN alone, no statistically significant differences were observed between the  
122 2 treatment groups of combination ZYBAN and NTS (n = 197) and ZYBAN alone (n = 193) in  
123 the plasma concentrations of bupropion or its active metabolites at weeks 3 and 6.

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

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

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

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

155 **Renal:** There is limited information on the pharmacokinetics of bupropion in patients with  
156 renal impairment. The elimination of the major metabolites of bupropion may be reduced by  
157 impaired renal function (see PRECAUTIONS: Renal Impairment).

158 **Left Ventricular Dysfunction:** During a chronic dosing study with bupropion in  
159 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on  
160 x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared to  
161 healthy normal volunteers, was revealed.

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

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

## 174 **CLINICAL TRIALS**

175 The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in  
176 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1,940,  
177  $\geq 15$  cigarettes per day). In these studies, ZYBAN was used in conjunction with individual  
178 smoking cessation counseling.

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

184 Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase in  
185 the percentage of patients able to achieve 4-week abstinence (weeks 4 through 7). Treatment  
186 with ZYBAN at both 150 and 300 mg/day was significantly more effective than placebo in this  
187 study.

188 Table 1 presents quit rates over time in the multicenter trial by treatment group. The quit rates  
189 are the proportions of all persons initially enrolled (i.e., intent to treat analysis) who abstained  
190 from week 4 of the study through the specified week. Treatment with ZYBAN (150 or

191 300 mg/day) was more effective than placebo in helping patients achieve 4-week abstinence. In  
 192 addition, treatment with ZYBAN (7 weeks at 300 mg/day) was more effective than placebo in  
 193 helping patients maintain continuous abstinence through week 26 (6 months) of the study.

194

195 **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)

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

197

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

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

210



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

Abstinence From Week 4 Through Specified Week	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)
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)

212  
 213 When patients in this study were followed out to one year, the superiority of ZYBAN and the  
 214 combination of ZYBAN and NTS over placebo in helping patients to achieve abstinence from  
 215 smoking was maintained. The continuous abstinence rate was 30% (95% CI 24-35) in the  
 216 ZYBAN treated patients, and 33% (95% CI 27-39) for patients treated with the combination at  
 217 26 weeks compared with 13% (95% CI 7-18) in the placebo group. At 52 weeks, the continuous  
 218 abstinence rate was 23% (95% CI 18-28) in the ZYBAN treated patients, and 28% (95% CI  
 219 23-34) for patients treated with the combination, compared with 8% (95% CI 3-12) in the  
 220 placebo group. Although the treatment combination of ZYBAN and NTS displayed the highest  
 221 rates of continuous abstinence throughout the study, the quit rates for the combination were not  
 222 significantly higher ( $p>0.05$ ) than for ZYBAN alone.

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

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

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

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

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

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

251

252 **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)

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

## 254 **INDICATIONS AND USAGE**

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

## 256 **CONTRAINDICATIONS**

257 ZYBAN is contraindicated in patients with a seizure disorder.

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

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

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

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

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

## 273 **WARNINGS**

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

282 Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and  
283 others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of  
284 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events  
285 representing suicidal behavior or thinking (suicidality) during the first few months of treatment  
286 in those receiving antidepressants. The average risk of such events in patients receiving  
287 antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk  
288 among drugs, but a tendency toward an increase for almost all drugs studied. The risk of  
289 suicidality was most consistently observed in the MDD trials, but there were signals of risk  
290 arising from some trials in other psychiatric indications (obsessive compulsive disorder and  
291 social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown  
292 whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several  
293 months. It is also unknown whether the suicidality risk extends to adults.

294 **All pediatric patients being treated with antidepressants for any indication should be**  
295 **observed closely for clinical worsening, suicidality, and unusual changes in behavior,**  
296 **especially during the initial few months of a course of drug therapy, or at times of dose**  
297 **changes, either increases or decreases. Such observation would generally include at least**  
298 **weekly face-to-face contact with patients or their family members or caregivers during the**  
299 **first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at**  
300 **12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may**  
301 **be appropriate between face-to-face visits.**

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

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

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

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

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

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

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

341 **Patients should be made aware that ZYBAN contains the same active ingredient found**  
342 **in WELLBUTRIN, WELLBUTRIN SR, and WELLBUTRIN XL used to treat depression,**  
343 **and that ZYBAN should not be used in combination with WELLBUTRIN (bupropion**  
344 **hydrochloride), the immediate release formulation; WELLBUTRIN SR (bupropion**  
345 **hydrochloride), the sustained-release formulation; WELLBUTRIN XL (bupropion**

346 hydrochloride), the extended-release formulation; or any other medications that contain  
347 bupropion.

348

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

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

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

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

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

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

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

376 • the total daily dose of ZYBAN does *not* exceed 300 mg (the maximum recommended  
377 dose for smoking cessation), and

378 • the recommended daily dose for most patients (300 mg/day) is administered in divided  
379 doses (150 mg twice daily).

380 • No single dose should exceed 150 mg to avoid high peak concentrations of bupropion  
381 and/or its metabolites.

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

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

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

## 396 PRECAUTIONS

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

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

407 **Insomnia:** In the dose-response smoking cessation trial, 29% of patients treated with  
408 150 mg/day of ZYBAN and 35% of patients treated with 300 mg/day of ZYBAN experienced  
409 insomnia, compared to 21% of placebo-treated patients. Symptoms were sufficiently severe to  
410 require discontinuation of treatment in 0.6% of patients treated with ZYBAN and none of the  
411 patients treated with placebo.

412 In the comparative trial, 40% of the patients treated with 300 mg/day of ZYBAN, 28% of the  
413 patients treated with 21 mg/day of NTS, and 45% of the patients treated with the combination of  
414 ZYBAN and NTS experienced insomnia compared to 18% of placebo-treated patients.  
415 Symptoms were sufficiently severe to require discontinuation of treatment in 0.8% of patients  
416 treated with ZYBAN and none of the patients in the other 3 treatment groups.

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

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

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

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

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

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

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

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

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

464 **Renal Impairment:** There is limited information on the pharmacokinetics of bupropion in  
465 patients with renal impairment. Bupropion is extensively metabolized in the liver to active  
466 metabolites, which are further metabolized and subsequently excreted by the kidneys. ZYBAN  
467 should be used with caution in patients with renal impairment and a reduced frequency of dosing  
468 should be considered as the metabolites of bupropion may accumulate in such patients to a  
469 greater extent than usual. The patient should be closely monitored for possible adverse effects  
470 that could indicate high drug or metabolite levels.

471 **Information for Patients:** Although ZYBAN is not indicated for treatment of depression, it  
472 contains the same active ingredient as the antidepressant medications WELLBUTRIN,  
473 WELLBUTRIN SR, and WELLBUTRIN XL. Prescribers or other health professionals should  
474 inform patients, their families, and their caregivers about the benefits and risks associated with  
475 treatment with ZYBAN and should counsel them in its appropriate use. A patient Medication  
476 Guide About Using Antidepressants in Children and Teenagers is available for ZYBAN. The  
477 prescriber or health professional should instruct patients, their families, and their caregivers to  
478 read the Medication Guide and should assist them in understanding its contents. Patients should  
479 be given the opportunity to discuss the contents of the Medication Guide and to obtain answers  
480 to any questions they may have. The complete text of the Medication Guide is reprinted at the  
481 end of this document. Additional important information concerning ZYBAN is provided in a  
482 tear-off leaflet entitled "Patient Information" at the end of this labeling.

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

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

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

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

502 **Drug Interactions:** In vitro studies indicate that bupropion is primarily metabolized to  
503 hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug



504 interaction between ZYBAN and drugs that are substrates or inhibitors of the CYP2B6  
505 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies  
506 suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir,  
507 ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been  
508 performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not  
509 appear to be produced by the cytochrome P450 isoenzymes. Few systemic data have been  
510 collected on the metabolism of ZYBAN following concomitant administration with other drugs  
511 or, alternatively, the effect of concomitant administration of ZYBAN on the metabolism of other  
512 drugs.

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

516 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in  
517 humans. However, following chronic administration of bupropion, 100 mg t.i.d to 8 healthy male  
518 volunteers for 14 days, there was no evidence of induction of its own metabolism. Because  
519 bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical  
520 activity. In particular, certain drugs may induce the metabolism of bupropion (e.g.,  
521 carbamazepine, phenobarbital, phenytoin), while other drugs may inhibit the metabolism of  
522 bupropion (e.g., cimetidine). The effects of concomitant administration of cimetidine on the  
523 pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male  
524 volunteers. Following oral administration of two 150-mg ZYBAN tablets with and without  
525 800 mg of cimetidine, the pharmacokinetics of bupropion and its hydroxy metabolite were  
526 unaffected. However, there were 16% and 32% increases, respectively, in the AUC and  $C_{max}$  of  
527 the combined moieties of threohydro- and erythrohydro- bupropion.

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

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

544 receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original  
545 medication should be considered, particularly for those concomitant medications with a narrow  
546 therapeutic index.

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

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

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

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

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

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

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

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

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

579 **Pregnancy: Teratogenic Effects:** Pregnancy Category C: In studies conducted in rats and  
580 rabbits, bupropion was administered orally at doses up to 450 and 150 mg/kg/day, respectively  
581 (approximately 14 and 10 times the maximum recommended human dose [MRHD], respectively,  
582 on a mg/m<sup>2</sup> basis), during the period of organogenesis. No clear evidence of teratogenic activity  
583 was found in either species; however, in rabbits, slightly increased incidences of fetal

584 malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day,  
585 approximately 2 times the MRHD on a mg/m<sup>2</sup> basis) and greater. Decreased fetal weights were  
586 seen at 50 mg/kg and greater.

587 When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately  
588 10 times the MRHD on a mg/m<sup>2</sup> basis) prior to mating and throughout pregnancy and lactation,  
589 there were no apparent adverse effects on offspring development.

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

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

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

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

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

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

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

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

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

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

639 **Adverse Events Associated With the Discontinuation of Treatment:** Adverse events  
640 were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 patients  
641 treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events  
642 leading to discontinuation of treatment with ZYBAN included nervous system disturbances  
643 (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

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

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

652 **Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated  
653 With ZYBAN:** Table 4 enumerates selected treatment-emergent adverse events from the  
654 dose-response trial that occurred at an incidence of 1% or more and were more common in  
655 patients treated with ZYBAN compared to those treated with placebo. Table 5 enumerates  
656 selected treatment-emergent adverse events from the comparative trial that occurred at an  
657 incidence of 1% or more and were more common in patients treated with ZYBAN, NTS, or the  
658 combination of ZYBAN and NTS compared to those treated with placebo. Reported adverse  
659 events were classified using a COSTART-based dictionary.

660

661 **Table 4. 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

662 \* Selected adverse events with an incidence of at least 1% of patients treated with ZYBAN  
 663 and more frequent than in the placebo group.  
 664

**Table 5. 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) %
<b>Body</b>				
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
<b>Cardiovascular</b>				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
<b>Digestive</b>				
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
<b>Musculoskeletal</b>				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
<b>Nervous system</b>				
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
<b>Respiratory</b>				
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

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

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

669

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

#### 675 **Other Events Observed During the Clinical Development and Postmarketing**

676 **Experience of Bupropion:** In addition to the adverse events noted above, the following  
677 events have been reported in clinical trials and postmarketing experience with the  
678 sustained-release formulation of bupropion in depressed patients and in nondepressed smokers,  
679 as well as in clinical trials and postmarketing clinical experience with the immediate-release  
680 formulation of bupropion.

681 Adverse events for which frequencies are provided below occurred in clinical trials with  
682 bupropion sustained-release. The frequencies represent the proportion of patients who  
683 experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled  
684 studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced  
685 an adverse event requiring discontinuation of treatment in an open-label surveillance study with  
686 bupropion sustained-release tablets (n = 3,100). All treatment-emergent adverse events are  
687 included except those listed in Tables 4 and 5, those events listed in other safety-related sections  
688 of the insert, those adverse events subsumed under COSTART terms that are either overly  
689 general or excessively specified so as to be uninformative, those events not reasonably associated  
690 with the use of the drug, and those events that were not serious and occurred in fewer than  
691 2 patients.

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

694 occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to  
695 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

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

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

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

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

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

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

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

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

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

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

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



734 **Special Senses:** Frequent was amblyopia. Infrequent were accommodation abnormality  
735 and dry eye. Also observed were deafness, diplopia, and mydriasis.

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

## 740 **DRUG ABUSE AND DEPENDENCE**

741 ZYBAN is likely to have a low abuse potential.

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

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

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

## 761 **OVERDOSAGE**

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

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

772 **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation.  
773 Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first  
774 48 hours post-ingestion. General supportive and symptomatic measures are also recommended.  
775 Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with  
776 appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in  
777 symptomatic patients.

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

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

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

## 789 **DOSAGE AND ADMINISTRATION**

790 **Usual Dosage for Adults:** The recommended and maximum dose of ZYBAN is 300 mg/day,  
791 given as 150 mg twice daily. Dosing should begin at 150 mg/day given every day for the first  
792 3 days, followed by a dose increase for most patients to the recommended usual dose of  
793 300 mg/day. There should be an interval of at least 8 hours between successive doses. Doses  
794 above 300 mg/day should not be used (see WARNINGS). ZYBAN should be swallowed whole  
795 and not crushed, divided, or chewed. Treatment with ZYBAN should be initiated **while the**  
796 **patient is still smoking**, since approximately 1 week of treatment is required to achieve  
797 steady-state blood levels of bupropion. Patients should set a "target quit date" within the first  
798 2 weeks of treatment with ZYBAN, generally in the second week. Treatment with ZYBAN  
799 should be continued for 7 to 12 weeks; longer treatment should be guided by the relative benefits  
800 and risks for individual patients. If a patient has not made significant progress towards  
801 abstinence by the seventh week of therapy with ZYBAN, it is unlikely that he or she will quit  
802 during that attempt, and treatment should probably be discontinued. Conversely, a patient who  
803 successfully quits after 7 to 12 weeks of treatment should be considered for ongoing therapy with  
804 ZYBAN. Dose tapering of ZYBAN is not required when discontinuing treatment. It is important  
805 that patients continue to receive counseling and support throughout treatment with ZYBAN, and  
806 for a period of time thereafter.

807 **Individualization of Therapy:** Patients are more likely to quit smoking and remain abstinent  
808 if they are seen frequently and receive support from their physicians or other health care  
809 professionals. It is important to ensure that patients read the instructions provided to them and  
810 have their questions answered. Physicians should review the patient's overall smoking cessation

811 program that includes treatment with ZYBAN. Patients should be advised of the importance of  
812 participating in the behavioral interventions, counseling, and/or support services to be used in  
813 conjunction with ZYBAN. See information for patients at the end of the package insert.

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

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

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

#### 826 **Combination Treatment With ZYBAN and a Nicotine Transdermal System (NTS):**

827 Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation. The  
828 prescriber should review the complete prescribing information for both ZYBAN and NTS before  
829 using combination treatment. See also CLINICAL TRIALS for methods and dosing used in the  
830 ZYBAN and NTS combination trial. Monitoring for treatment-emergent hypertension in patients  
831 treated with the combination of ZYBAN and NTS is recommended.

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

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

#### 841 **HOW SUPPLIED**

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

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

847

848

849

### **Medication Guide** **ZYBAN<sup>®</sup> (zi ban)**

850 (bupropion hydrochloride) Sustained-Release Tablets  
851 About Using Antidepressants in Children and Teenagers  
852

853 **What is the most important information I should know if my child is being prescribed an**  
854 **antidepressant?**  
855

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

- 858 1. There is a risk of suicidal thoughts or actions
  - 859 2. How to try to prevent suicidal thoughts or actions in your child
  - 860 3. You should watch for certain signs if your child is taking an antidepressant
  - 861 4. There are benefits and risks when using antidepressants
- 862

863 **1. There is a Risk of Suicidal Thoughts or Actions**  
864

865 Children and teenagers sometimes think about suicide, and many report trying to kill themselves.  
866

867 Antidepressants increase suicidal thoughts and actions in some children and teenagers. But  
868 suicidal thoughts and actions can also be caused by depression, a serious medical condition that  
869 is commonly treated with antidepressants. Thinking about killing yourself or trying to kill  
870 yourself is called *suicidality* or *being suicidal*.  
871

872 A large study combined the results of 24 different studies of children and teenagers with  
873 depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an  
874 antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients  
875 became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4  
876 out of every 100 patients became suicidal.  
877

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

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

883 If any of these are present, make sure you tell your healthcare provider before your child takes an  
884 antidepressant.  
885

886 **2. How to Try to Prevent Suicidal Thoughts and Actions**  
887

888 To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her  
889 or his moods or actions, especially if the changes occur suddenly. Other important people in your

890 child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers,  
891 and other important people). The changes to look out for are listed in Section 3, on what to watch  
892 for.

893  
894 Whenever an antidepressant is started or its dose is changed, pay close attention to your child.  
895 After starting an antidepressant, your child should generally see his or her healthcare provider:

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

901  
902 You should call your child's healthcare provider between visits if needed.

### 903 904 **3. You Should Watch For Certain Signs if Your Child is Taking an Antidepressant**

905  
906 Contact your child's healthcare provider *right away* if your child exhibits any of the following  
907 signs for the first time, or they seem worse, or worry you, your child, or your child's teacher:

- 908 • Thoughts about suicide or dying
- 909 • Attempts to commit suicide
- 910 • New or worse depression
- 911 • New or worse anxiety
- 912 • Feeling very agitated or restless
- 913 • Panic attacks
- 914 • Difficulty sleeping (insomnia)
- 915 • New or worse irritability
- 916 • Acting aggressive, being angry, or violent
- 917 • Acting on dangerous impulses
- 918 • An extreme increase in activity and talking
- 919 • Other unusual changes in behavior or mood

920  
921 Never let your child stop taking an antidepressant without first talking to his or her healthcare  
922 provider. Stopping an antidepressant suddenly can cause other symptoms.

### 923 924 **4. There are Benefits and Risks When Using Antidepressants**

925  
926 Antidepressants are used to treat depression and other illnesses. Depression and other illnesses  
927 can lead to suicide. In some children and teenagers, treatment with an antidepressant increases  
928 suicidal thinking or actions. It is important to discuss all the risks of treating depression and also

929 the risks of not treating it. You and your child should discuss all treatment choices with your  
930 healthcare provider, not just the use of antidepressants.

931

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

933

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

936

937 For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine  
938 (Prozac<sup>®</sup>)\*, sertraline (Zoloft<sup>®</sup>)\*, fluvoxamine, and clomipramine (Anafranil<sup>®</sup>)\*.

939

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

942

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

944

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

949

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

952

953 This Medication Guide has been approved by the U.S. Food and Drug Administration for all  
954 antidepressants.

955

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957

958



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972  
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974

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**PHARMACIST--DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT. ALSO  
PROVIDE AN APPROVED MEDICATION GUIDE ABOUT USING  
ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS.**

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975 -----  
976 **Patient Information**

977 **ZYBAN<sup>®</sup> (zi ban)**

978 **(bupropion hydrochloride) Sustained-Release Tablets**  
979

980 **Read the Patient Information that comes with ZYBAN before you start taking ZYBAN and**  
981 **each time you get a refill.** There may be new information. This leaflet does not take the place of  
982 talking with your doctor about your medical condition or your treatment. You and your doctor  
983 should discuss ZYBAN as part of your plan to stop smoking.  
984

985 **What is the most important information I should know about ZYBAN?**

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

- 987
- 988 • with certain medical problems.
  - 989 • who take certain medicines.

990 The chance of having seizures increases with higher doses of ZYBAN. For more information,  
991 see the sections “Who should not take ZYBAN?” and “What should I tell my doctor before using  
992 ZYBAN?” Tell your doctor about all of your medical conditions and all the medicines you take.  
993 **Do not take any other medicines while you are using ZYBAN unless your doctor has said it**  
994 **is okay to take them.**  
995

996 **If you have a seizure while taking ZYBAN, stop taking the tablets and call your doctor**  
997 **right away.** Do not take ZYBAN again if you have a seizure.  
998

999 **What is important information I should know and share with my family about taking**  
1000 **antidepressants?**

1001 Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the  
1002 antidepressant medications WELLBUTRIN<sup>®</sup>, WELLBUTRIN SR<sup>®</sup>, and WELLBUTRIN XL<sup>®</sup>.  
1003 Therefore, you should be aware of the following information. Patients taking antidepressants,  
1004 and their families, should watch out for worsening depression or thoughts of suicide. Also watch  
1005 out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable,

1006 hostile, aggressive, impulsive, severely restless, overly excited and hyperactive, not being able to  
1007 sleep, or other unusual changes in behavior. If this happens, especially at the beginning of  
1008 antidepressant treatment or after a change in dose, call your doctor.

1009  
1010 A patient Medication Guide will be provided to you with each prescription of ZYBAN entitled  
1011 "About Using Antidepressants in Children and Teenagers." ZYBAN is not approved for use in  
1012 children and teenagers.

1013  
1014 **What is ZYBAN?**

1015 ZYBAN is a prescription medicine to help people quit smoking. Studies have shown that more  
1016 than one third of people quit smoking for at least 1 month while taking ZYBAN and participating  
1017 in a patient support program. For many patients, ZYBAN reduces withdrawal symptoms and the  
1018 urge to smoke. ZYBAN should be used with a patient support program. It is important to  
1019 participate in the behavioral program, counseling, or other support program your health care  
1020 professional recommends.

1021  
1022 **Who should not take ZYBAN?**

1023 **Do not take ZYBAN if you:**

- 1024 • have or had a seizure disorder or epilepsy.
- 1025 • **are taking WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, or any other**  
1026 **medicines that contain bupropion hydrochloride.** Bupropion is the same active ingredient  
1027 that is in ZYBAN.
- 1028 • drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these  
1029 make you sleepy) or benzodiazepines and you stop using them all of a sudden.
- 1030 • have taken within the last 14 days medicine for depression called a monoamine oxidase  
1031 inhibitor (MAOI), such as NARDIL<sup>®\*</sup> (phenelzine sulfate), PARNATE<sup>®</sup> (tranylcypromine  
1032 sulfate), or MARPLAN<sup>®\*</sup> (isocarboxazid).
- 1033 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1034 • are allergic to the active ingredient in ZYBAN, bupropion, or to any of the inactive  
1035 ingredients. See the end of this leaflet for a complete list of ingredients in ZYBAN.

1036  
1037 **Can I take ZYBAN if I have mild-to-moderate chronic bronchitis and/or emphysema (also**  
1038 **called chronic obstructive pulmonary disease or COPD)?**

1039 Yes, ZYBAN combined with a behavior modification program has been shown to help people  
1040 with COPD quit smoking. It is important to participate in the behavior program, counseling, or  
1041 other support program your health care professional recommends.

1042  
1043 **What should I tell my doctor before using ZYBAN?**

- 1044 • **Tell your doctor about your medical conditions.** Tell your doctor if you:



- 1045 • **are pregnant or plan to become pregnant.** It is not known if ZYBAN can harm your  
1046 unborn baby. If you can use ZYBAN while you are pregnant, talk to your doctor about  
1047 how you can be on the Bupropion Pregnancy Registry.
- 1048 • **are breastfeeding.** ZYBAN passes through your milk. It is not known if ZYBAN can  
1049 harm your baby.
- 1050 • **have liver problems,** especially cirrhosis of the liver.
- 1051 • have kidney problems.
- 1052 • have an eating disorder such as anorexia nervosa or bulimia.
- 1053 • have had a head injury.
- 1054 • have had a seizure (convulsion, fit).
- 1055 • have a tumor in your nervous system (brain or spine).
- 1056 • have had a heart attack, heart problems, or high blood pressure.
- 1057 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1058 • drink a lot of alcohol.
- 1059 • abuse prescription medicines or street drugs.
- 1060
- 1061 • **Tell your doctor about all the medicines you take,** including prescription and non-  
1062 prescription medicines, vitamins, and herbal supplements. Many medicines increase your  
1063 chances of getting seizures or other serious side effects if you take them while you are using  
1064 ZYBAN.
- 1065

1066 ZYBAN has not been studied in children under the age of 18 years.

1067

#### 1068 **How should I take ZYBAN?**

- 1069 • Take ZYBAN exactly as prescribed by your doctor.
- 1070 • **Do not chew, cut, or crush ZYBAN Tablets.** You must swallow the tablets whole. **Tell**  
1071 **your doctor if you cannot swallow medicine tablets.**
- 1072 • Take ZYBAN at the same time each day.
- 1073 • Take your doses of ZYBAN at least 8 hours apart.
- 1074 • If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and  
1075 take your next tablet at the regular time. **This is very important.** Too much ZYBAN can  
1076 increase your chance of having a seizure.
- 1077 • If you take too much ZYBAN, or overdose, call your local emergency room or poison  
1078 control center right away.
- 1079 • **Do not take any other medicines while using ZYBAN unless your doctor has told you it**  
1080 **is okay.**
- 1081 • Do not change your dose or stop taking ZYBAN without talking with your doctor first.
- 1082

#### 1083 **How long should I take ZYBAN?**

1084 Most people should take ZYBAN for at least 7 to 12 weeks. Some people may need to take  
1085 ZYBAN for a longer period of time to assist in their smoking cessation efforts. Follow your  
1086 doctor's instructions.

1087

### 1088 **When should I stop smoking?**

1089 It takes about 1 week for ZYBAN to reach the right levels in your body to be effective. So, to  
1090 maximize your chance of quitting, you should not stop smoking until you have been taking  
1091 ZYBAN for 1 week. You should set a date to stop smoking during the second week you're  
1092 taking ZYBAN.

1093

### 1094 **Can I smoke while taking ZYBAN?**

1095 It is not physically dangerous to smoke and use ZYBAN at the same time. However, continuing  
1096 to smoke after the date you set to stop smoking will seriously reduce your chance of breaking  
1097 your smoking habit.

1098

### 1099 **Can ZYBAN be used at the same time as nicotine patches?**

1100 Yes, ZYBAN and nicotine patches can be used at the same time but should only be used together  
1101 under the supervision of your doctor. Using ZYBAN and nicotine patches together may raise  
1102 your blood pressure, sometimes severely. Tell your doctor if you are planning to use nicotine  
1103 replacement therapy because your doctor will probably want to check your blood pressure  
1104 regularly to make sure that it stays within acceptable levels.

1105

1106 **DO NOT SMOKE AT ANY TIME** if you are using a nicotine patch or any other nicotine  
1107 product along with ZYBAN. It is possible to get too much nicotine and have serious side effects.

1108

### 1109 **What should I avoid while taking ZYBAN?**

- 1110 • Do not drink a lot of alcohol while taking ZYBAN. If you usually drink a lot of alcohol, talk  
1111 with your doctor before suddenly stopping. If you suddenly stop drinking alcohol, you may  
1112 increase your chance of having seizures.
- 1113 • Do not drive a car or use heavy machinery until you know how ZYBAN affects you.  
1114 ZYBAN can impair your ability to perform these tasks.

1115

### 1116 **What are possible side effects of ZYBAN?**

- 1117 • **Seizures.** Some patients get seizures while taking ZYBAN. **If you have a seizure while**  
1118 **taking ZYBAN, stop taking the tablets and call your doctor right away.** Do not take  
1119 ZYBAN again if you have a seizure.
- 1120 • **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes  
1121 severe, while taking ZYBAN. The chance of high blood pressure may be increased if you  
1122 also use nicotine replacement therapy (for example, a nicotine patch) to help you stop  
1123 smoking (see "Can ZYBAN be used at the same time as nicotine patches?").

- 1124 • **Severe allergic reactions: Stop taking ZYBAN and call your doctor right away** if you get  
1125 a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the  
1126 eyes, swelling of the lips or tongue, chest pain, or have trouble breathing. These could be  
1127 signs of a serious allergic reaction.
- 1128 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or behaviors while  
1129 taking ZYBAN, including delusions (believe you are someone else), hallucinations (seeing or  
1130 hearing things that are not there), paranoia (feeling that people are against you), or feeling  
1131 confused. If this happens to you, call your doctor.

1132

1133 The most common side effects of ZYBAN are dry mouth and difficulty sleeping. These side  
1134 effects are generally mild and often disappear after a few weeks. If you have difficulty sleeping,  
1135 do not take your medicine too close to bedtime.

1136

1137 Tell your doctor right away about any side effects that bother you.

1138

1139 These are not all the side effects of ZYBAN. For a complete list, ask your doctor or pharmacist.

1140

#### 1141 **How should I store ZYBAN?**

- 1142 • Store ZYBAN at room temperature. Store out of direct sunlight. Keep ZYBAN in its tightly  
1143 closed bottle.
- 1144 • ZYBAN may have an odor.

1145

#### 1146 **General Information about ZYBAN.**

- 1147 • Medicines are sometimes prescribed for conditions that are not mentioned in patient  
1148 information leaflets. Do not use ZYBAN for a condition for which it was not prescribed. Do  
1149 not give ZYBAN to other people, even if they have the same symptoms you have. It may  
1150 harm them. Keep ZYBAN out of the reach of children.

1151

1152 This leaflet summarizes important information about ZYBAN. For more information, talk with  
1153 your doctor. You can ask your doctor or pharmacist for information about ZYBAN that is written  
1154 for health professionals.

1155

#### 1156 **What are the ingredients in ZYBAN?**

1157 Active ingredient: bupropion hydrochloride.

1158

1159 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate,  
1160 microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. The tablets  
1161 are printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake  
1162 and FD&C Red No. 40 Lake.

1163

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1165 Lambert Company; Marplan<sup>®</sup>/Oxford Pharmaceutical Services, Inc.

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