

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYBAN safely and effectively. See full prescribing information for ZYBAN.

ZYBAN (bupropion hydrochloride) Sustained-Release Tablets, for oral use

Initial U.S. Approval: 1985

### WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.1)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.2)
- Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)

### RECENT MAJOR CHANGES

Dosage and Administration, Use of ZYBAN with Reversible MAOIs Such as Linezolid or Methylene Blue (2.8)	03/2014
Contraindications (4)	03/2014
Warnings and Precautions, Angle-closure Glaucoma (5.7)	08/2014

### INDICATIONS AND USAGE

ZYBAN is an aminoketone agent indicated as an aid to smoking cessation treatment. (1)

### DOSAGE AND ADMINISTRATION

- Starting dose: 150 mg per day for first 3 days. (2.1)
- General: Increase dose gradually to reduce seizure risk. (2.1, 5.3)
- Begin dosing one week before quit day. (2.1)
- After 3 days, increase the dose to 300 mg per day, given as 150 mg twice daily at an interval of at least 8 hours. (2.1)
- May be used with a nicotine transdermal system. (2.5)
- Moderate to severe hepatic impairment: 150 mg every other day. (2.6, 8.7)
- Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.6, 8.7)
- Renal impairment: Consider reducing the dose and/or frequency. (2.7, 8.6)

### DOSAGE FORMS AND STRENGTHS

- Tablets: 150 mg. (3)

### CONTRAINDICATIONS

- Seizure disorder. (4, 5.3)
- Current or prior diagnosis of bulimia or anorexia nervosa. (4, 5.3)
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3)
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with ZYBAN or within 14 days of stopping treatment with ZYBAN. Do not use ZYBAN within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start

ZYBAN in a patient who is being treated with linezolid or intravenous methylene blue. (4, 7.6)

- Known hypersensitivity to bupropion or other ingredients of ZYBAN. (4, 5.8)

### WARNINGS AND PRECAUTIONS

- Seizure risk: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 300 mg. Discontinue if seizure occurs. (4, 5.3, 7.3)
- Hypertension: ZYBAN can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment, especially if used with nicotine replacement. (5.4)
- Activation of mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms. (5.5)
- Psychosis and other neuropsychiatric reactions. Instruct patients to contact a healthcare professional if reactions occur. (5.6)
- Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7)

### ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 5\%$  and  $\geq 1\%$  more than placebo rate) are: insomnia, rhinitis, dry mouth, dizziness, nervous disturbance, anxiety, nausea, constipation, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- CYP2B6 inducers: Dose increase may be necessary if coadministered with CYP2B6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital and phenytoin) based on clinical response, but should not exceed the maximum recommended dose. (7.1)
- Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide). Consider dose reduction when using with bupropion. (7.2)
- Drugs that lower seizure threshold: Dose ZYBAN with caution. (5.3, 7.3)
- Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with ZYBAN. (7.4)
- MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with ZYBAN. (7.6)
- Drug-laboratory test interactions: ZYBAN can cause false-positive urine test results for amphetamines. (7.8)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND** 3 **BEHAVIORS**

#### 4 **NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR** 5 **SMOKING CESSATION**

6        **Serious neuropsychiatric reactions have occurred in patients taking ZYBAN<sup>®</sup> for**  
 7 **smoking cessation [see Warnings and Precautions (5.1)]. The majority of these reactions**  
 8 **occurred during bupropion treatment, but some occurred in the context of discontinuing**  
 9 **treatment. In many cases, a causal relationship to bupropion treatment is not certain,**  
 10 **because depressed mood may be a symptom of nicotine withdrawal. However, some of the**  
 11 **cases occurred in patients taking ZYBAN who continued to smoke.**

12        **The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has**  
 13 **been demonstrated to increase the likelihood of abstinence from smoking for as long as 6**  
 14 **months compared with treatment with placebo. The health benefits of quitting smoking are**  
 15 **immediate and substantial.**

#### 16 **SUICIDALITY AND ANTIDEPRESSANT DRUGS**

17        **Although ZYBAN is not indicated for treatment of depression, it contains the same**  
 18 **active ingredient as the antidepressant medications WELLBUTRIN<sup>®</sup>,**  
 19 **WELLBUTRIN<sup>®</sup> SR, and WELLBUTRIN XL<sup>®</sup>. Antidepressants increased the risk of**  
 20 **suicidal thoughts and behavior in children, adolescents, and young adults in short-term**  
 21 **trials. These trials did not show an increase in the risk of suicidal thoughts and behavior**  
 22 **with antidepressant use in subjects over age 24; there was a reduction in risk with**  
 23 **antidepressant use in subjects aged 65 and older [see Warnings and Precautions (5.2)].**

24        **In patients of all ages who are started on antidepressant therapy, monitor closely for**  
 25 **worsening, and for emergence of suicidal thoughts and behaviors. Advise families and**  
 26 **caregivers of the need for close observation and communication with the prescriber [see**  
 27 **Warnings and Precautions (5.2)].**

## 28 **1 INDICATIONS AND USAGE**

29        **ZYBAN is indicated as an aid to smoking cessation treatment.**

30 **2 DOSAGE AND ADMINISTRATION**

31 **2.1 Usual Dosage**

32 Treatment with ZYBAN should be initiated **before** the patient’s planned quit day, **while**  
33 **the patient is still smoking**, because it takes approximately 1 week of treatment to achieve  
34 steady-state blood levels of bupropion. The patient should set a “target quit date” within the first  
35 2 weeks of treatment with ZYBAN.

36 Dosing: To minimize the risk of seizure:

- 37 • Begin dosing with one 150-mg tablet per day for 3 days.
- 38 • Increase dose to 300 mg/day given as one 150-mg tablet twice each day with an  
39 interval of at least 8 hours between each dose.
- 40 • Do not exceed 300 mg/day.

41 ZYBAN should be swallowed whole and not crushed, divided, or chewed, as this may  
42 lead to an increased risk of adverse effects including seizures [*see Warnings and Precautions*  
43 (5.3)].

44 ZYBAN may be taken with or without food [*see Clinical Pharmacology (12.3)*].

45 **2.2 Duration of Treatment**

46 Treatment with ZYBAN should be continued for 7 to 12 weeks. If the patient has not quit  
47 smoking after 7 to 12 weeks, it is unlikely that he or she will quit during that attempt so  
48 treatment with ZYBAN should probably be discontinued and the treatment plan reassessed. The  
49 goal of therapy with ZYBAN is complete abstinence.

50 Discuss discontinuing treatment with ZYBAN after 12 weeks if the patient feels ready  
51 but consider whether the patient may benefit from ongoing treatment. Patients who successfully  
52 quit after 12 weeks of treatment but do not feel ready to discontinue treatment should be  
53 considered for ongoing therapy with ZYBAN; longer treatment should be guided by the relative  
54 benefits and risks for individual patients.

55 It is important that patients continue to receive counseling and support throughout  
56 treatment with ZYBAN and for a period of time thereafter.

57 **2.3 Individualization of Therapy**

58 Patients are more likely to quit smoking and remain abstinent if they are seen frequently  
59 and receive support from their physicians or other healthcare professionals. It is important to  
60 ensure that patients read the instructions provided to them and have their questions answered.  
61 Physicians should review the patient’s overall smoking cessation program that includes treatment  
62 with ZYBAN. Patients should be advised of the importance of participating in the behavioral  
63 interventions, counseling, and/or support services to be used in conjunction with ZYBAN [*see*  
64 *Medication Guide*].

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

## 70 **2.4 Maintenance**

71 Tobacco dependence is a chronic condition. Some patients may need on-going treatment.  
72 Whether to continue treatment with ZYBAN for periods longer than 12 weeks for smoking  
73 cessation must be determined for individual patients.

## 74 **2.5 Combination Treatment with ZYBAN and a Nicotine Transdermal System** 75 **(NTS)**

76 Combination treatment with ZYBAN and NTS may be prescribed for smoking cessation.  
77 The prescriber should review the complete prescribing information for both ZYBAN and NTS  
78 before using combination treatment [*see Clinical Studies (14)*]. Monitoring for  
79 treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS is  
80 recommended.

## 81 **2.6 Dose Adjustment in Patients with Hepatic Impairment**

82 In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the  
83 maximum dose should not exceed 150 mg every other day. In patients with mild hepatic  
84 impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing  
85 [*see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)*].

## 86 **2.7 Dose Adjustment in Patients with Renal Impairment**

87 Consider reducing the dose and/or frequency of ZYBAN in patients with renal  
88 impairment (Glomerular Filtration Rate less than 90 mL/min) [*see Use in Specific Populations*  
89 *(8.6), Clinical Pharmacology (12.3)*].

## 90 **2.8 Use of ZYBAN with Reversible MAOIs Such as Linezolid or Methylene Blue**

91 Do not start ZYBAN in a patient who is being treated with a reversible MAOI such as  
92 linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive  
93 reactions [*see Contraindications (4), Drug Interactions (7.6)*].

94 In some cases, a patient already receiving therapy with ZYBAN may require urgent  
95 treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or  
96 intravenous methylene blue treatment are not available and the potential benefits of linezolid or  
97 intravenous methylene blue treatment are judged to outweigh the risks of hypertensive reactions  
98 in a particular patient, ZYBAN should be stopped promptly, and linezolid or intravenous  
99 methylene blue can be administered. The patient should be monitored for 2 weeks or until 24  
100 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first.  
101 Therapy with ZYBAN may be resumed 24 hours after the last dose of linezolid or intravenous  
102 methylene blue.

103 The risk of administering methylene blue by non-intravenous routes (such as oral tablets  
104 or by local injection) or in intravenous doses much lower than 1 mg/kg with ZYBAN is unclear.  
105 The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use  
106 [*see Contraindications (4), Drug Interactions (7.6)*].

107 **3 DOSAGE FORMS AND STRENGTHS**

108 150 mg – purple, round, biconvex, film-coated, sustained-release tablets printed with  
109 “ZYBAN 150”.

110 **4 CONTRAINDICATIONS**

- 111 • ZYBAN is contraindicated in patients with a seizure disorder.
- 112 • ZYBAN is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia  
113 nervosa as a higher incidence of seizures was observed in such patients treated with the  
114 immediate-release formulation of bupropion [*see Warnings and Precautions (5.3)*].
- 115 • ZYBAN is contraindicated in patients undergoing abrupt discontinuation of alcohol,  
116 benzodiazepines, barbiturates, and antiepileptic drugs [*see Warnings and Precautions (5.3),*  
117 *Drug Interactions (7.3)*].
- 118 • The use of MAOIs (intended to treat psychiatric disorders) concomitantly with ZYBAN or  
119 within 14 days of discontinuing treatment with ZYBAN is contraindicated. There is an  
120 increased risk of hypertensive reactions when ZYBAN is used concomitantly with MAOIs.  
121 The use of ZYBAN within 14 days of discontinuing treatment with an MAOI is also  
122 contraindicated. Starting ZYBAN in a patient treated with reversible MAOIs such as  
123 linezolid or intravenous methylene blue is contraindicated [*see Dosage and Administration*  
124 *(2.8), Warnings and Precautions (5.4), Drug Interactions (7.6)*].
- 125 • ZYBAN is contraindicated in patients with a known hypersensitivity to bupropion or other  
126 ingredients of ZYBAN. Anaphylactoid/anaphylactic reactions and Stevens-Johnson  
127 syndrome have been reported [*see Warnings and Precautions (5.8)*].

128 **5 WARNINGS AND PRECAUTIONS**

129 **5.1 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation**

130 **Treatment**

131 Serious neuropsychiatric symptoms have been reported in patients taking ZYBAN for  
132 smoking cessation. These have included changes in mood (including depression and mania),  
133 psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression,  
134 anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide [*see*  
135 *Boxed Warning, Adverse Reactions (6.2)*]. Observe patients for the occurrence of  
136 neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions  
137 occur.

138 In many of these cases, a causal relationship to bupropion treatment is not certain,  
139 because depressed mood can be a symptom of nicotine withdrawal. However, some of the cases  
140 occurred in patients taking ZYBAN who continued to smoke.

141 The risks of ZYBAN should be weighed against the benefits of its use. ZYBAN has been  
142 demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months  
143 compared with treatment with placebo. The health benefits of quitting smoking are immediate  
144 and substantial.

145 **5.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young**  
 146 **Adults**

147 Patients with MDD, both adult and pediatric, may experience worsening of their  
 148 depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual  
 149 changes in behavior, whether or not they are taking antidepressant medications, and this risk may  
 150 persist until significant remission occurs. Suicide is a known risk of depression and certain other  
 151 psychiatric disorders, and these disorders themselves are the strongest predictors of suicide.  
 152 There has been a long-standing concern that antidepressants may have a role in inducing  
 153 worsening of depression and the emergence of suicidality in certain patients during the early  
 154 phases of treatment.

155 Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective  
 156 serotonin reuptake inhibitors [SSRIs] and others) show that these drugs increase the risk of  
 157 suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to  
 158 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase  
 159 in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24;  
 160 there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

161 The pooled analyses of placebo-controlled trials in children and adolescents with MDD,  
 162 obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24  
 163 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of  
 164 placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of  
 165 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000  
 166 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency  
 167 toward an increase in the younger subjects for almost all drugs studied. There were differences in  
 168 absolute risk of suicidality across the different indications, with the highest incidence in MDD.  
 169 The risk differences (drug vs. placebo), however, were relatively stable within age strata and  
 170 across indications. These risk differences (drug-placebo difference in the number of cases of  
 171 suicidality per 1,000 subjects treated) are provided in Table 1.

172  
 173 **Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled**  
 174 **Placebo-controlled Trials of Antidepressants in Pediatric and Adult Subjects**

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

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

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

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

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

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

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

### **5.3 Seizure**

ZYBAN can cause seizure. The risk of seizure is dose-related. The dose of ZYBAN should not exceed 300 mg per day [see *Dosage and Administration (2.1)*]. Discontinue ZYBAN and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with ZYBAN. ZYBAN is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see *Contraindications (4), Drug Interactions (7.3)*]. The following conditions can also increase the risk of seizure: severe head

216 injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant  
217 use of other medications that lower the seizure threshold (e.g., other bupropion products,  
218 antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic  
219 disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), use of  
220 illicit drugs (e.g., cocaine), or abuse or misuse of prescription drugs such as CNS stimulants.  
221 Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic  
222 drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines,  
223 sedative/hypnotics, or opiates.

224 **Incidence of Seizure with Bupropion Use:** Doses for smoking cessation should not  
225 exceed 300 mg per day. The seizure rate associated with doses of sustained-release bupropion in  
226 depressed patients up to 300 mg per day is approximately 0.1% (1/1,000) and increases to  
227 approximately 0.4% (4/1000) at doses up to 400 mg per day.

228 The risk of seizure can be reduced if the dose of ZYBAN for smoking cessation does not  
229 exceed 300 mg per day, given as 150 mg twice daily, and titration rate is gradual.

#### 230 **5.4 Hypertension**

231 Treatment with ZYBAN can result in elevated blood pressure and hypertension. Assess  
232 blood pressure before initiating treatment with ZYBAN, and monitor periodically during  
233 treatment. The risk of hypertension is increased if ZYBAN is used concomitantly with MAOIs or  
234 other drugs that increase dopaminergic or noradrenergic activity [*see Contraindications (4)*].

235 Data from a comparative trial of ZYBAN, nicotine transdermal system (NTS), the  
236 combination of ZYBAN plus NTS, and placebo as an aid to smoking cessation suggest a higher  
237 incidence of treatment-emergent hypertension in patients treated with the combination of  
238 ZYBAN and NTS. In this trial, 6.1% of subjects treated with the combination of ZYBAN and  
239 NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects  
240 treated with ZYBAN, NTS, and placebo, respectively. The majority of these subjects had  
241 evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of  
242 ZYBAN and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due  
243 to hypertension compared with none of the subjects treated with ZYBAN or placebo. Monitoring  
244 of blood pressure is recommended in patients who receive the combination of bupropion and  
245 nicotine replacement.

246 In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive  
247 heart failure (N = 36), bupropion was associated with an exacerbation of pre-existing  
248 hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no  
249 controlled trials assessing the safety of bupropion in patients with a recent history of myocardial  
250 infarction or unstable cardiac disease.

#### 251 **5.5 Activation of Mania/Hypomania**

252 Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk  
253 appears to be increased in patients with bipolar disorder or who have risk factors for bipolar  
254 disorder. There were no reports of activation of psychosis or mania in clinical trials with

255 ZYBAN conducted in nondepressed smokers. Bupropion is not approved for use in treating  
256 bipolar depression.

## 257 **5.6 Psychosis and Other Neuropsychiatric Reactions**

258 Depressed patients treated with bupropion in depression trials have had a variety of  
259 neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis,  
260 concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of  
261 bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal  
262 of treatment. Instruct patients to contact a healthcare professional if such reactions occur.

263 In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of  
264 neuropsychiatric side effects was generally comparable to placebo. However, in the  
265 postmarketing experience, patients taking ZYBAN to quit smoking have reported similar types  
266 of neuropsychiatric symptoms to those reported by patients in the clinical trials of bupropion for  
267 depression.

## 268 **5.7 Angle-closure Glaucoma**

269 The pupillary dilation that occurs following use of many antidepressant drugs including  
270 bupropion may trigger an angle-closure attack in a patient with anatomically narrow angles who  
271 does not have a patent iridectomy.

## 272 **5.8 Hypersensitivity Reactions**

273 Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion.  
274 Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring  
275 medical treatment. In addition, there have been rare, spontaneous postmarketing reports of  
276 erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with  
277 bupropion. Instruct patients to discontinue ZYBAN and consult a healthcare provider if they  
278 develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest  
279 pain, edema, and shortness of breath) during treatment.

280 There are reports of arthralgia, myalgia, fever with rash and other serum sickness-like  
281 symptoms suggestive of delayed hypersensitivity.

## 282 **6 ADVERSE REACTIONS**

283 The following adverse reactions are discussed in greater detail in other sections of the  
284 labeling:

- 285 • Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [*see Boxed*  
286 *Warning, Warnings and Precautions (5.1)*]
- 287 • Suicidal thoughts and behaviors in adolescents and young adults [*see Boxed Warning,*  
288 *Warnings and Precautions (5.2)*]
- 289 • Seizure [*see Warnings and Precautions (5.3)*]
- 290 • Hypertension [*see Warnings and Precautions (5.4)*]
- 291 • Activation of mania or hypomania [*see Warnings and Precautions (5.5)*]
- 292 • Psychosis and other neuropsychiatric reactions [*see Warnings and Precautions (5.6)*]
- 293 • Angle-closure glaucoma [*see Warnings and Precautions (5.7)*]

294 • Hypersensitivity reactions [see Warnings and Precautions (5.8)]

## 295 **6.1 Clinical Trials Experience**

296 Because clinical trials are conducted under widely varying conditions, adverse reaction  
297 rates observed in the clinical trials of a drug cannot be directly compared with rates in the  
298 clinical trials of another drug and may not reflect the rates observed in clinical practice.

299 Adverse Reactions Leading to Discontinuation of Treatment: Adverse reactions  
300 were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 subjects  
301 treated with ZYBAN and 5% of the 313 patients treated with placebo. The more common events  
302 leading to discontinuation of treatment with ZYBAN included nervous system disturbances  
303 (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

304 Commonly Observed Adverse Reactions: The most commonly observed adverse  
305 reactions consistently associated with the use of ZYBAN were dry mouth and insomnia. The  
306 incidence of dry mouth and insomnia may be related to the dose of ZYBAN. The occurrence of  
307 these adverse reactions may be minimized by reducing the dose of ZYBAN. In addition,  
308 insomnia may be minimized by avoiding bedtime doses.

309 Adverse reactions reported in the dose-response and comparator trials are presented in  
310 Table 2 and Table 3, respectively. Reported adverse reactions were classified using a  
311 COSTART-based dictionary.

312

313 **Table 2. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater**  
314 **Frequency than Placebo in the Dose-response Trial**

<b>Adverse Reaction</b>	<b>ZYBAN 100 to 300 mg/day (n = 461) %</b>	<b>Placebo (n = 150) %</b>
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

315

316 **Table 3. Adverse Reactions Reported by at Least 1% of Subjects on Active Treatment and**  
317 **at a Greater Frequency than Placebo in the Comparator Trial**

<b>Adverse Experience (COSTART Term)</b>	<b>ZYBAN 300 mg/day (n = 243) %</b>	<b>Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %</b>	<b>ZYBAN and NTS (n = 244) %</b>	<b>Placebo (n = 159) %</b>
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
Digestive				

Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous system				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				
Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction <sup>a</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

318 <sup>a</sup> Subjects randomized to ZYBAN or placebo received placebo patches.

319

320 Adverse reactions in a 1-year maintenance trial and a 12-week COPD trial with ZYBAN

321 were quantitatively and qualitatively similar to those observed in the dose-response and

322 comparator trials.

323 Other Adverse Reactions Observed during the Clinical Development of  
324 Bupropion: In addition to the adverse reactions noted above, the following adverse reactions  
325 have been reported in clinical trials with the sustained-release formulation of bupropion in  
326 depressed subjects and in nondepressed smokers, as well as in clinical trials with the  
327 immediate-release formulation of bupropion.

328 Adverse reaction frequencies represent the proportion of subjects who experienced a  
329 treatment-emergent adverse reaction on at least one occasion in placebo-controlled trials for  
330 depression (n = 987) or smoking cessation (n = 1,013), or subjects who experienced an adverse  
331 reaction requiring discontinuation of treatment in an open-label surveillance trial with bupropion  
332 sustained-release tablets (n = 3,100). All treatment-emergent adverse reactions are included  
333 except those listed in Tables 2 and 3, those listed in other safety-related sections of the  
334 prescribing information, those subsumed under COSTART terms that are either overly general or  
335 excessively specific so as to be uninformative, those not reasonably associated with the use of  
336 the drug, and those that were not serious and occurred in fewer than 2 subjects.

337 Adverse reactions are further categorized by body system and listed in order of  
338 decreasing frequency according to the following definitions of frequency: Frequent adverse  
339 reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions  
340 are those occurring in 1/100 to 1/1,000 subjects, while rare events are those occurring in less than  
341 1/1,000 subjects.

342 *Body (General)*: Frequent were asthenia, fever, and headache. Infrequent were chills,  
343 inguinal hernia, and photosensitivity. Rare was malaise.

344 *Cardiovascular*: Infrequent were flushing, migraine, postural hypotension, stroke,  
345 tachycardia, and vasodilation. Rare was syncope.

346 *Digestive*: Frequent were dyspepsia and vomiting. Infrequent were abnormal liver  
347 function, bruxism, dysphagia, gastric reflux, gingivitis, jaundice, and stomatitis.

348 *Hemic and Lymphatic*: Infrequent was ecchymosis.

349 *Metabolic and Nutritional*: Infrequent were edema and peripheral edema.

350 *Musculoskeletal*: Infrequent were leg cramps and twitching.

351 *Nervous System*: Frequent were agitation, depression, and irritability. Infrequent  
352 were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory,  
353 depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,  
354 paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and  
355 hypomania.

356 *Respiratory*: Rare was bronchospasm.

357 *Skin*: Frequent was sweating.

358 *Special Senses*: Frequent was blurred vision or diplopia. Infrequent were  
359 accommodation abnormality and dry eye.

360 *Urogenital*: Frequent was urinary frequency. Infrequent were impotence, polyuria,  
361 and urinary urgency.

## 362 **6.2 Postmarketing Experience**

363 The following adverse reactions have been identified during post-approval use of  
364 ZYBAN and are not described elsewhere in the label. Because these reactions are reported  
365 voluntarily from a population of uncertain size, it is not always possible to reliably estimate their  
366 frequency or establish a relationship to drug exposure.

367 Body (General): Arthralgia, myalgia, and fever with rash and other symptoms  
368 suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness [*see*  
369 *Warnings and Precautions (5.8)*].

370 Cardiovascular: Cardiovascular disorder, complete AV block, extrasystoles,  
371 hypotension, myocardial infarction, phlebitis, and pulmonary embolism.

372 Digestive: Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis,  
373 increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool  
374 abnormality.

375 Endocrine: Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic  
376 hormone.

377 Hemic and Lymphatic: Anemia, leukocytosis, leukopenia, lymphadenopathy,  
378 pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with  
379 hemorrhagic or thrombotic complications, were observed when bupropion was coadministered  
380 with warfarin.

381 Metabolic and Nutritional: Glycosuria.

382 Musculoskeletal: Arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle  
383 weakness.

384 Nervous System: Abnormal electroencephalogram (EEG), aggression, akinesia,  
385 aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria,  
386 extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction,  
387 neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive  
388 dyskinesia.

389 Respiratory: Pneumonia.

390 Skin: Alopecia, angioedema, exfoliative dermatitis, hirsutism, and Stevens-Johnson  
391 syndrome.

392 Special Senses: Deafness, increased intraocular pressure, and mydriasis.

393 Urogenital: Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia,  
394 menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary  
395 retention, urinary tract disorder, and vaginitis.

## 396 **7 DRUG INTERACTIONS**

### 397 **7.1 Potential for Other Drugs to Affect ZYBAN**

398 Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the  
399 potential exists for drug interactions between ZYBAN and drugs that are inhibitors or inducers of  
400 CYP2B6.

401 Inhibitors of CYP2B6: Ticlopidine and Clopidogrel: Concomitant treatment with these  
402 drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on  
403 clinical response, dosage adjustment of ZYBAN may be necessary when coadministered with  
404 CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see *Clinical Pharmacology (12.3)*].

405 Inducers of CYP2B6: Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment  
406 with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of  
407 ZYBAN may be necessary when coadministered with ritonavir, lopinavir, or efavirenz [see  
408 *Clinical Pharmacology (12.3)*] but should not exceed the maximum recommended dose.

409 Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these  
410 drugs may induce the metabolism of bupropion and may decrease bupropion exposure [see  
411 *Clinical Pharmacology (12.3)*]. If bupropion is used concomitantly with a CYP inducer, it may  
412 be necessary to increase the dose of bupropion, but the maximum recommended dose should not  
413 be exceeded.

## 414 **7.2 Potential for ZYBAN to Affect Other Drugs**

415 Drugs Metabolized by CYP2D6: Bupropion and its metabolites  
416 (erythrohydrobupropion, threo hydrobupropion, hydroxybupropion) are CYP2D6 inhibitors.  
417 Therefore, coadministration of ZYBAN with drugs that are metabolized by CYP2D6 can  
418 increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain  
419 antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine,  
420 and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g.,  
421 metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used  
422 concomitantly with ZYBAN, it may be necessary to decrease the dose of these CYP2D6  
423 substrates, particularly for drugs with a narrow therapeutic index.

424 Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen)  
425 theoretically could have reduced efficacy when administered concomitantly with inhibitors of  
426 CYP2D6 such as bupropion. Patients treated concomitantly with ZYBAN and such drugs may  
427 require increased doses of the drug [see *Clinical Pharmacology (12.3)*].

## 428 **7.3 Drugs that Lower Seizure Threshold**

429 Use extreme caution when coadministering ZYBAN with other drugs that lower seizure  
430 threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or  
431 systemic corticosteroids). Use low initial doses and increase the dose gradually [see  
432 *Contraindications (4), Warnings and Precautions (5.3)*].

## 433 **7.4 Dopaminergic Drugs (Levodopa and Amantadine)**

434 Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has  
435 been reported when bupropion was coadministered with levodopa or amantadine. Adverse  
436 reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and  
437 dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use  
438 caution when administering ZYBAN concomitantly with these drugs.

## 439 **7.5 Use with Alcohol**

440 In postmarketing experience, there have been rare reports of adverse neuropsychiatric  
441 events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with  
442 ZYBAN. The consumption of alcohol during treatment with ZYBAN should be minimized or  
443 avoided.

#### 444 **7.6 MAO Inhibitors**

445 Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of  
446 MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive  
447 reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that  
448 the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days  
449 should elapse between discontinuation of an MAOI and initiation of treatment with ZYBAN.  
450 Conversely, at least 14 days should be allowed after stopping ZYBAN before starting an MAOI  
451 intended to treat psychiatric disorders [*see Dosage and Administration (2.8), Contraindications*  
452 *(4)*].

#### 453 **7.7 Smoking Cessation**

454 Physiological changes resulting from smoking cessation, with or without treatment with  
455 ZYBAN, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g.,  
456 theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

#### 457 **7.8 Drug-Laboratory Test Interactions**

458 False-positive urine immunoassay screening tests for amphetamines have been reported  
459 in patients taking bupropion. This is due to lack of specificity of some screening tests. False-  
460 positive test results may result even following discontinuation of bupropion therapy.  
461 Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion  
462 from amphetamines.

### 463 **8 USE IN SPECIFIC POPULATIONS**

#### 464 **8.1 Pregnancy**

465 Pregnancy Category C.

466 Risk Summary: Data from epidemiological studies of pregnant women exposed to  
467 bupropion in the first trimester indicate no increased risk of congenital malformations overall.  
468 All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major  
469 malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity  
470 was found in reproductive developmental studies conducted in rats and rabbits; however, in  
471 rabbits, slightly increased incidences of fetal malformations and skeletal variations were  
472 observed at doses approximately 2 times the maximum recommended human dose (MRHD) and  
473 greater and decreased fetal weights were seen at doses three times the MRHD and greater.  
474 ZYBAN should be used during pregnancy only if the potential benefit justifies the potential risk  
475 to the fetus.

476 Clinical Considerations: Pregnant smokers should be encouraged to attempt cessation  
477 using educational and behavioral interventions before pharmacological approaches are used.

478 Human Data: Data from the international bupropion Pregnancy Registry (675 first  
479 trimester exposures) and a retrospective cohort study using the United Healthcare database  
480 (1,213 first trimester exposures) did not show an increased risk for malformations overall.

481 No increased risk for cardiovascular malformations overall has been observed after  
482 bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular  
483 malformations in pregnancies with exposure to bupropion in the first trimester from the  
484 international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester  
485 maternal bupropion exposures), which is similar to the background rate of cardiovascular  
486 malformations (approximately 1%). Data from the United Healthcare database and a case-control  
487 study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular  
488 malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an  
489 increased risk for cardiovascular malformations overall after bupropion exposure during the first  
490 trimester.

491 Study findings on bupropion exposure during the first trimester and risk for left  
492 ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions  
493 regarding a possible association. The United Healthcare database lacked sufficient power to  
494 evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR =  
495 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk  
496 for LVOTO.

497 Study findings on bupropion exposure during the first trimester and risk for ventricular  
498 septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible  
499 association. The Slone Epidemiology Study found an increased risk for VSD following first  
500 trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not  
501 find increased risk for any other cardiovascular malformations studied (including LVOTO as  
502 above). The NBDPS and United Healthcare database study did not find an association between  
503 first trimester maternal bupropion exposure and VSD.

504 For the findings of LVOTO and VSD, the studies were limited by the small number of  
505 exposed cases, inconsistent findings among studies, and the potential for chance findings from  
506 multiple comparisons in case control studies.

507 Animal Data: In studies conducted in rats and rabbits, bupropion was administered  
508 orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day,  
509 respectively (approximately 15 and 10 times the MRHD respectively, on a mg per m<sup>2</sup> basis). No  
510 clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly  
511 increased incidences of fetal malformations and skeletal variations were observed at the lowest  
512 dose tested (25 mg per kg per day, approximately 2 times the MRHD on a mg per m<sup>2</sup> basis) and  
513 greater. Decreased fetal weights were observed at 50 mg per kg and greater.

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

### 517 **8.3 Nursing Mothers**

518 Bupropion and its metabolites are present in human milk. In a lactation study of 10  
519 women, levels of orally dosed bupropion and its active metabolites were measured in expressed  
520 milk. The average daily infant exposure (assuming 150 mL per kg daily consumption) to  
521 bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Exercise  
522 caution when ZYBAN is administered to a nursing woman.

#### 523 **8.4 Pediatric Use**

524 Safety and effectiveness in the pediatric population have not been established [*see Boxed*  
525 *Warning, Warnings and Precautions (5.2)*].

#### 526 **8.5 Geriatric Use**

527 Of the approximately 6,000 subjects who participated in clinical trials with bupropion  
528 sustained-release tablets (depression and smoking cessation trials), 275 were aged  $\geq 65$  years and  
529 47 were aged  $\geq 75$  years. In addition, several hundred subjects aged  $\geq 65$  years participated in  
530 clinical trials using the immediate-release formulation of bupropion (depression trials). No  
531 overall differences in safety or effectiveness were observed between these subjects and younger  
532 subjects. Reported clinical experience has not identified differences in responses between the  
533 elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled  
534 out.

535 Bupropion is extensively metabolized in the liver to active metabolites, which are further  
536 metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients  
537 with impaired renal function. Because elderly patients are more likely to have decreased renal  
538 function, it may be necessary to consider this factor in dose selection; it may be useful to monitor  
539 renal function [*see Dosage and Administration (2.7), Use in Specific Populations (8.6), Clinical*  
540 *Pharmacology (12.3)*].

#### 541 **8.6 Renal Impairment**

542 Consider a reduced dose and/or dosing frequency of ZYBAN in patients with renal  
543 impairment (Glomerular Filtration Rate: less than 90 mL per min). Bupropion and its metabolites  
544 are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor  
545 closely for adverse reactions that could indicate high bupropion or metabolite exposures [*see*  
546 *Dosage and Administration (2.7), Clinical Pharmacology (12.3)*].

#### 547 **8.7 Hepatic Impairment**

548 In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the  
549 maximum dose of ZYBAN is 150 mg every other day. In patients with mild hepatic impairment  
550 (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [*see Dosage*  
551 *and Administration (2.6), Clinical Pharmacology (12.3)*].

### 552 **9 DRUG ABUSE AND DEPENDENCE**

#### 553 **9.1 Controlled Substance**

554 Bupropion is not a controlled substance.

#### 555 **9.2 Abuse**

556 Humans: Controlled clinical trials conducted in normal volunteers, in subjects with a  
557 history of multiple drug abuse, and in depressed subjects showed some increase in motor activity  
558 and agitation/excitement, often typical of central stimulant activity.

559 In a population of individuals experienced with drugs of abuse, a single oral dose of  
560 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the  
561 Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a  
562 score greater than placebo but less than 15mg of the Schedule II stimulant dextroamphetamine  
563 on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug  
564 liking which are often associated with abuse potential.

565 Findings in clinical trials, however, are not known to reliably predict the abuse potential  
566 of drugs. Nonetheless, evidence from single-dose trials does suggest that the recommended daily  
567 dosage of bupropion when administered orally in divided doses is not likely to be significantly  
568 reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (that could not be  
569 tested because of the risk of seizure) might be modestly attractive to those who abuse CNS  
570 stimulant drugs.

571 ZYBAN is intended for oral use only. The inhalation of crushed tablets or injection of  
572 dissolved bupropion has been reported. Seizures and/or cases of death have been reported when  
573 bupropion has been administered intranasally or by parenteral injection.

574 Animals: Studies in rodents and primates demonstrated that bupropion exhibits some  
575 pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase  
576 locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding  
577 in several schedule-controlled behavior paradigms. In primate models assessing the positive  
578 reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats,  
579 bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug  
580 discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

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

## 584 **10 OVERDOSAGE**

### 585 **10.1 Human Overdose Experience**

586 Overdoses of up to 30 grams or more of bupropion have been reported. Seizure was  
587 reported in approximately one-third of all cases. Other serious reactions reported with overdoses  
588 of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG  
589 changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever,  
590 muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been  
591 reported mainly when bupropion was part of multiple drug overdoses.

592 Although most patients recovered without sequelae, deaths associated with overdoses of  
593 bupropion alone have been reported in patients ingesting large doses of the drug. Multiple

594 uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported  
595 in these patients.

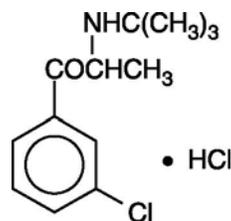
## 596 **10.2 Overdosage Management**

597 Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone  
598 numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR).  
599 Call 1-800-222-1222 or refer to [www.poison.org](http://www.poison.org).

600 There are no known antidotes for bupropion. In case of an overdose, provide supportive  
601 care, including close medical supervision and monitoring. Consider the possibility of multiple  
602 drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm  
603 and vital signs. Induction of emesis is not recommended.

## 604 **11 DESCRIPTION**

605 ZYBAN (bupropion hydrochloride) Sustained-Release Tablets are a non-nicotine aid to  
606 smoking cessation. ZYBAN is chemically unrelated to nicotine or other agents currently used in  
607 the treatment of nicotine addiction. Initially developed and marketed as an antidepressant  
608 (WELLBUTRIN [bupropion hydrochloride] Tablets and WELLBUTRIN SR [bupropion  
609 hydrochloride] Sustained-Release Tablets), ZYBAN is also chemically unrelated to tricyclic,  
610 tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its  
611 structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is  
612 designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride.  
613 The molecular weight is 276.2. The molecular formula is  $C_{13}H_{18}ClNO \cdot HCl$ . Bupropion  
614 hydrochloride powder is white, crystalline, and highly soluble in water. It has a bitter taste and  
615 produces the sensation of local anesthesia on the oral mucosa. The structural formula is:  
616



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

## 625 **12 CLINICAL PHARMACOLOGY**

### 626 **12.1 Mechanism of Action**

627 The exact mechanism by which ZYBAN enhances the ability of patients to abstain from  
628 smoking is not known but is presumed to be related to noradrenergic and/or dopaminergic

629 mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine  
630 and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit  
631 monoamine oxidase.

### 632 **12.3 Pharmacokinetics**

633 Bupropion is a racemic mixture. The pharmacological activity and pharmacokinetics of  
634 the individual enantiomers have not been studied. The mean elimination half-life ( $\pm$ SD) of  
635 bupropion after chronic dosing is 21 ( $\pm$ 9) hours, and steady-state plasma concentrations of  
636 bupropion are reached within 8 days.

637 Absorption: The absolute bioavailability of ZYBAN in humans has not been determined  
638 because an intravenous formulation for human use is not available. However, it appears likely  
639 that only a small proportion of any orally administered dose reaches the systemic circulation  
640 intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

641 In humans, following oral administration of ZYBAN, peak plasma concentration ( $C_{\max}$ )  
642 of bupropion is usually achieved within 3 hours.

643 ZYBAN can be taken with or without food. Bupropion  $C_{\max}$  and AUC was increased by  
644 11% to 35%, and 16% to 19%, respectively, when ZYBAN was administered with food to  
645 healthy volunteers in three trials. The food effect is not considered clinically significant.

646 Distribution: In vitro tests show that bupropion is 84% bound to human plasma proteins  
647 at concentrations up to 200 mcg per mL. The extent of protein binding of the hydroxybupropion  
648 metabolite is similar to that for bupropion; whereas, the extent of protein binding of the  
649 threohydrobupropion metabolite is about half that seen with bupropion.

650 Metabolism: Bupropion is extensively metabolized in humans. Three metabolites are  
651 active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of  
652 bupropion, and the amino-alcohol isomers, threohydrobupropion and erythrohydrobupropion,  
653 which are formed via reduction of the carbonyl group. In vitro findings suggest that CYP2B6 is  
654 the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450  
655 enzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion  
656 side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is  
657 then excreted as the major urinary metabolite. The potency and toxicity of the metabolites  
658 relative to bupropion have not been fully characterized. However, it has been demonstrated in an  
659 antidepressant screening test in mice that hydroxybupropion is one-half as potent as bupropion,  
660 while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion.  
661 This may be of clinical importance, because the plasma concentrations of the metabolites are as  
662 high as or higher than those of bupropion.

663 Following a single-dose administration of ZYBAN in humans,  $C_{\max}$  of hydroxybupropion  
664 occurs approximately 6 hours post-dose and is approximately 10 times the peak level of the  
665 parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20  
666 ( $\pm$ 5) hours and its AUC at steady state is about 17 times that of bupropion. The times to peak  
667 concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar  
668 to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer,

669 33 ( $\pm 10$ ) and 37 ( $\pm 13$ ) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of  
670 bupropion, respectively.

671 Bupropion and its metabolites exhibit linear kinetics following chronic administration of  
672 300 to 450 mg per day.

673 **Elimination:** Following oral administration of 200 mg of  $^{14}\text{C}$ -bupropion in humans, 87%  
674 and 10% of the radioactive dose were recovered in the urine and feces, respectively. Only 0.5%  
675 of the oral dose was excreted as unchanged bupropion.

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

682 **Renal Impairment:** There is limited information on the pharmacokinetics of  
683 bupropion in patients with renal impairment. An inter-trial comparison between normal subjects  
684 and subjects with end-stage renal failure demonstrated that the parent drug  $C_{\text{max}}$  and AUC values  
685 were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion  
686 metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage  
687 renal failure. A second trial, comparing normal subjects and subjects with moderate-to-severe  
688 renal impairment (GFR  $30.9 \pm 10.8$  mL per min), showed that after a single 150-mg dose of  
689 sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects  
690 with impaired renal function while levels of the hydroxybupropion and  
691 threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is  
692 extensively metabolized in the liver to active metabolites, which are further metabolized and  
693 subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion  
694 may be reduced by impaired renal function. ZYBAN should be used with caution in patients with  
695 renal impairment and a reduced frequency and/or dose should be considered [*see Use in Specific*  
696 *Populations (8.6)*].

697 **Hepatic Impairment:** The effect of hepatic impairment on the pharmacokinetics of  
698 bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease  
699 and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of  
700 hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in  
701 8 healthy volunteers ( $32 \pm 14$  hours versus  $21 \pm 5$  hours, respectively). Although not statistically  
702 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be  
703 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life  
704 for bupropion and the other metabolites in the 2 groups were minimal.

705 The second trial demonstrated no statistically significant differences in the  
706 pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild-to-moderate  
707 hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in  
708 some of the pharmacokinetic parameters for bupropion ( $\text{AUC}$ ,  $C_{\text{max}}$ , and  $T_{\text{max}}$ ) and its active

709 metabolites ( $t_{1/2}$ ) in subjects with mild-to-moderate hepatic cirrhosis. In 8 subjects with severe  
710 hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites  
711 were seen (Table 4).

712

713 **Table 4. Pharmacokinetics of Bupropion and Metabolites in Patients with Severe Hepatic**  
714 **Cirrhosis: Ratio Relative to Healthy Matched Controls**

	<b>C<sub>max</sub></b>	<b>AUC</b>	<b>t<sub>1/2</sub></b>	<b>T<sub>max</sub><sup>a</sup></b>
Bupropion	1.69	3.12	1.43	0.5 h
Hydroxybupropion	0.31	1.28	3.88	19 h
Threo/erythrohydrobupropion amino alcohol	0.69	2.48	1.96	20 h

715 <sup>a</sup> = Difference.

716

717 **Smokers:** The effects of cigarette smoking on the pharmacokinetics of bupropion  
718 were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and  
719 17 were nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there  
720 were no statistically significant differences in C<sub>max</sub>, half-life, T<sub>max</sub>, AUC, or clearance of  
721 bupropion or its major metabolites between smokers and nonsmokers.

722 In a trial comparing the treatment combination of ZYBAN and NTS versus ZYBAN  
723 alone, no statistically significant differences were observed between the 2 treatment groups of  
724 combination ZYBAN and NTS (n = 197) and ZYBAN alone (n = 193) in the plasma  
725 concentrations of bupropion or its active metabolites at Weeks 3 and 6.

726 **Left Ventricular Dysfunction:** During a chronic dosing trial with bupropion in  
727 14 depressed subjects with left ventricular dysfunction (history of CHF or an enlarged heart on  
728 x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its metabolites,  
729 compared with healthy volunteers.

730 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have  
731 not been fully characterized, but an exploration of steady-state bupropion concentrations from  
732 several depression efficacy trials involving subjects dosed in a range of 300 to 750 mg per day,  
733 on a 3-times-daily schedule, revealed no relationship between age (18 to 83 years) and plasma  
734 concentration of bupropion. A single-dose pharmacokinetic trial demonstrated that the  
735 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger  
736 subjects. These data suggest there is no prominent effect of age on bupropion concentration;  
737 however, another single- and multiple-dose pharmacokinetics trial suggested that the elderly are  
738 at increased risk for accumulation of bupropion and its metabolites [*see Use in Specific*  
739 *Populations (8.5)*].

740 **Gender:** Pooled analysis of bupropion pharmacokinetic data from 90 healthy male  
741 and 90 healthy female volunteers revealed no sex-related differences in the peak plasma  
742 concentrations of bupropion. The mean systemic exposure (AUC) was approximately 13%

743 higher in male volunteers compared with female volunteers. The clinical significance of this  
744 finding is unknown.

745 **Drug Interactions: Potential for Other Drugs to Affect ZYBAN:** In vitro studies  
746 indicate that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore,  
747 the potential exists for drug interactions between ZYBAN and drugs that are inhibitors or  
748 inducers of CYP2B6. In addition, in vitro studies suggest that paroxetine, sertraline,  
749 norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion.

750 **Inhibitors of CYP2B6: Ticlopidine, Clopidogrel:** In a trial in healthy male  
751 volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures  
752 ( $C_{max}$  and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for  
753 ticlopidine, respectively. The exposures ( $C_{max}$  and AUC) of hydroxybupropion were decreased  
754 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This  
755 effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

756 **Prasugrel:** Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects,  
757 prasugrel increased bupropion  $C_{max}$  and AUC values by 14% and 18%, respectively, and  
758 decreased  $C_{max}$  and AUC values of hydroxybupropion, an active metabolite of bupropion, by  
759 32% and 24%, respectively.

760 **Cimetidine:** The threohydrobupropion metabolite of bupropion does not appear  
761 to be produced by cytochrome P450 enzymes. The effects of concomitant administration of  
762 cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24  
763 healthy young male volunteers. Following oral administration of bupropion 300 mg with and  
764 without cimetidine 800 mg, the pharmacokinetics of bupropion and hydroxybupropion were  
765 unaffected. However, there were 16% and 32% increases in the AUC and  $C_{max}$ , respectively, of  
766 the combined moieties of threohydrobupropion and erythrohydrobupropion.

767 **Citalopram:** Citalopram did not affect the pharmacokinetics of bupropion and its  
768 3 metabolites.

769 **Inducers of CYP2B6: Ritonavir and Lopinavir:** In a healthy volunteer trial,  
770 ritonavir 100 mg twice daily reduced the AUC and  $C_{max}$  of bupropion by 22% and 21%,  
771 respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the  
772 threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

773 In a second healthy volunteer trial, ritonavir at a dose of 600 mg twice daily decreased  
774 the AUC and the  $C_{max}$  of bupropion by 66% and 62%, respectively. The exposure of the  
775 hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by  
776 50%, and the erythrohydrobupropion decreased by 68%.

777 In another healthy volunteer trial, lopinavir 400 mg/ritonavir 100 mg twice daily  
778 decreased bupropion AUC and  $C_{max}$  by 57%. The AUC and  $C_{max}$  of hydroxybupropion were  
779 decreased by 50% and 31%, respectively.

780 **Efavirenz:** In a trial in healthy volunteers, efavirenz 600 mg once daily for  
781 2 weeks reduced the AUC and  $C_{max}$  of bupropion by approximately 55% and 34%, respectively.

782 The AUC of hydroxybupropion was unchanged, whereas  $C_{max}$  of hydroxybupropion was  
783 increased by 50%.

784 *Carbamazepine, Phenobarbital, Phenytoin:* While not systematically studied,  
785 these drugs may induce the metabolism of bupropion.

786 Potential for ZYBAN to Affect Other Drugs: Animal data indicated that bupropion  
787 may be an inducer of drug-metabolizing enzymes in humans. In one trial, following chronic  
788 administration of bupropion 100 mg three times daily to 8 healthy male volunteers for 14 days,  
789 there was no evidence of induction of its own metabolism. Nevertheless, there may be potential  
790 for clinically important alterations of blood levels of co-administered drugs.

791 *Drugs Metabolized by CYP2D6:* In vitro, bupropion and its metabolites  
792 (erythrohydrobupropion, threo hydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a  
793 clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of  
794 CYP2D6, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased  
795 the  $C_{max}$ , AUC, and  $t_{1/2}$  of desipramine by an average of approximately 2-, 5-, and 2-fold,  
796 respectively. The effect was present for at least 7 days after the last dose of bupropion.  
797 Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally  
798 studied.

799 *Citalopram:* Although citalopram is not primarily metabolized by CYP2D6, in  
800 one trial bupropion increased the  $C_{max}$  and AUC of citalopram by 30% and 40%, respectively.

801 *Lamotrigine:* Multiple oral doses of bupropion had no statistically significant  
802 effects on the single-dose pharmacokinetics of lamotrigine in 12 healthy volunteers.

## 803 **13 NONCLINICAL TOXICOLOGY**

### 804 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

805 Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up  
806 to 300 and 150 mg per kg per day, respectively. These doses are approximately 10 and 2 times  
807 the MRHD, respectively, on a mg per  $m^2$  basis. In the rat study there was an increase in nodular  
808 proliferative lesions of the liver at doses of 100 to 300 mg per kg per day (approximately 3 to 10  
809 times the MRHD on a mg per  $m^2$  basis); lower doses were not tested. The question of whether or  
810 not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar  
811 liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver  
812 and other organs was seen in either study.

813 Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5  
814 strains in the Ames bacterial mutagenicity assay. Bupropion produced an increase in  
815 chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

816 A fertility study in rats at doses up to 300 mg per kg per day revealed no evidence of  
817 impaired fertility.

## 818 **14 CLINICAL STUDIES**

819 The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in  
820 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers ( $n = 1,940$ ,

821 greater than or equal to 15 cigarettes per day). In these trials, ZYBAN was used in conjunction  
822 with individual smoking cessation counseling.

823 The first trial was a dose-response trial conducted at 3 clinical centers. Subjects in this  
824 trial were treated for 7 weeks with 1 of 3 doses of ZYBAN (100, 150, or 300 mg per day) or  
825 placebo; quitting was defined as total abstinence during the last 4 weeks of treatment (Weeks 4  
826 through 7). Abstinence was determined by subject daily diaries and verified by carbon monoxide  
827 levels in expired air.

828 Results of this dose-response trial with ZYBAN demonstrated a dose-dependent increase  
829 in the percentage of subjects able to achieve 4-week abstinence (Weeks 4 through 7). Treatment  
830 with ZYBAN at both 150 and 300 mg per day was significantly more effective than placebo in  
831 this trial.

832 Table 5 presents quit rates over time in the multicenter trial by treatment group. The quit  
833 rates are the proportions of all subjects initially enrolled (i.e., intent-to-treat analysis) who  
834 abstained from Week 4 of the trial through the specified week. Treatment with ZYBAN (150 or  
835 300 mg per day) was more effective than placebo in helping subjects achieve 4-week abstinence.  
836 In addition, treatment with ZYBAN (7 weeks at 300 mg per day) was more effective than  
837 placebo in helping subjects maintain continuous abstinence through Week 26 (6 months) of the  
838 trial.

839

840 **Table 5. 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% <sup>a</sup> (20-35)	36% <sup>a</sup> (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25% <sup>a</sup> (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19% <sup>a</sup> (13-25)

841 <sup>a</sup> Significantly different from placebo ( $P \leq 0.05$ ).

842

843 The second trial was a comparator trial conducted at 4 clinical centers. Four treatments  
844 were evaluated: ZYBAN 300 mg per day, nicotine transdermal system (NTS) 21 mg per day,  
845 combination of ZYBAN 300 mg per day plus NTS 21 mg per day, and placebo. Subjects were  
846 treated for 9 weeks. Treatment with ZYBAN was initiated at 150 mg per day while the subject  
847 was still smoking and was increased after 3 days to 300 mg per day given as 150 mg twice daily.  
848 NTS 21 mg per day was added to treatment with ZYBAN after approximately 1 week when the

849 subject reached the target quit date. During Weeks 8 and 9 of the trial, NTS was tapered to 14  
 850 and 7 mg per day, respectively. Quitting, defined as total abstinence during Weeks 4 through 7,  
 851 was determined by subject daily diaries and verified by expired air carbon monoxide levels. In  
 852 this trial, subjects treated with any of the 3 treatments achieved greater 4-week abstinence rates  
 853 than subjects treated with placebo.

854 Table 6 presents quit rates over time by treatment group for the comparator trial.

855

856 **Table 6. Comparator 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)

857

858 When subjects in this trial were followed out to 1 year, the superiority of ZYBAN and the  
 859 combination of ZYBAN and NTS over placebo in helping them to achieve abstinence from  
 860 smoking was maintained. The continuous abstinence rate was 30% (95% CI: 24 to 35) in the  
 861 subjects treated with ZYBAN and 33% (95% CI: 27 to 39) for subjects treated with the  
 862 combination at 26 weeks compared with 13% (95% CI: 7 to 18) in the placebo group. At 52  
 863 weeks, the continuous abstinence rate was 23% (95% CI: 18 to 28) in the subjects treated with  
 864 ZYBAN and 28% (95% CI: 23 to 34) for subjects treated with the combination, compared with  
 865 8% (95% CI: 3 to 12) in the placebo group. Although the treatment combination of ZYBAN and  
 866 NTS displayed the highest rates of continuous abstinence throughout the trial, the quit rates for  
 867 the combination were not significantly higher ( $P>0.05$ ) than for ZYBAN alone.

868 The comparisons between ZYBAN, NTS, and combination treatment in this trial have not  
 869 been replicated, and, therefore should not be interpreted as demonstrating the superiority of any  
 870 of the active treatment arms over any other.

871 The third trial was a long-term maintenance trial conducted at 5 clinical centers. Subjects  
 872 in this trial received open-label ZYBAN 300 mg per day for 7 weeks. Subjects who quit smoking  
 873 while receiving ZYBAN (n = 432) were then randomized to ZYBAN 300 mg per day or placebo  
 874 for a total trial duration of 1 year. Abstinence from smoking was determined by subject  
 875 self-report and verified by expired air carbon monoxide levels. This trial demonstrated that at 6

876 months, continuous abstinence rates were significantly higher for subjects continuing to receive  
877 ZYBAN than for those switched to placebo ( $P<0.05$ ; 55% versus 44%).

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

881 Treatment with ZYBAN reduced withdrawal symptoms compared with placebo.  
882 Reductions on the following withdrawal symptoms were most pronounced: irritability,  
883 frustration, or anger; anxiety; difficulty concentrating; restlessness; and depressed mood or  
884 negative affect. Depending on the trial and the measure used, treatment with ZYBAN showed  
885 evidence of reduction in craving for cigarettes or urge to smoke compared with placebo.

886 Use in Patients with Chronic Obstructive Pulmonary Disease (COPD): ZYBAN  
887 was evaluated in a randomized, double-blind, comparator trial of 404 subjects with mild-to-  
888 moderate COPD defined as FEV<sub>1</sub> greater than or equal to 35%, FEV<sub>1</sub>/FVC less than or equal to  
889 70%, and a diagnosis of chronic bronchitis, emphysema, and/or small airways disease. Subjects  
890 aged 36 to 76 years were randomized to ZYBAN 300 mg per day (n = 204) or placebo (n = 200)  
891 and treated for 12 weeks. Treatment with ZYBAN was initiated at 150 mg per day for 3 days  
892 while the subject was still smoking and increased to 150 mg twice daily for the remaining  
893 treatment period. Abstinence from smoking was determined by subject daily diaries and verified  
894 by carbon monoxide levels in expired air. Quitters were defined as subjects who were abstinent  
895 during the last 4 weeks of treatment. Table 7 shows quit rates in the COPD Trial.

896

897 **Table 7. COPD Trial: Quit Rates by Treatment Group**

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

898 <sup>a</sup> Significantly different from placebo ( $P<0.05$ ).

899

## 900 **16 HOW SUPPLIED/STORAGE AND HANDLING**

901 ZYBAN Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple,  
902 round, biconvex, film-coated tablets printed with “ZYBAN 150” in bottles of 60 (NDC 0173-  
903 0556-02) tablets and the ZYBAN Advantage Pack<sup>®</sup> containing 1 bottle of 60 (NDC 0173-0556-  
904 01) tablets.

905 Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between  
906 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from light  
907 and moisture.

908 **17 PATIENT COUNSELING INFORMATION**

909 *Advise the patient to read the FDA-approved patient labeling (Medication Guide).*

910 Although ZYBAN is not indicated for treatment of depression, it contains the same active  
911 ingredient as the antidepressant medications WELLBUTRIN, WELLBUTRIN SR, and  
912 WELLBUTRIN XL. Inform patients, their families, and their caregivers about the benefits and  
913 risks associated with treatment with ZYBAN and counsel them in its appropriate use.

914 A patient Medication Guide about “Quitting Smoking, Quit-Smoking Medications,  
915 Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions,”  
916 “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal  
917 Thoughts or Actions,” and “What Other Important Information Should I Know About ZYBAN?”  
918 is available for ZYBAN. Instruct patients, their families, and their caregivers to read the  
919 Medication Guide and assist them in understanding its contents. Patients should be given the  
920 opportunity to discuss the contents of the Medication Guide and to obtain answers to any  
921 questions they may have. The complete text of the Medication Guide is reprinted at the end of  
922 this document.

923 Advise patients regarding the following issues and to alert their prescriber if these occur  
924 while taking ZYBAN.

925 **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment:**

926 Inform patients that quitting smoking, with or without ZYBAN, may be associated with nicotine  
927 withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing  
928 psychiatric illness. Furthermore, some patients have experienced changes in mood (including  
929 depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation,  
930 aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed  
931 suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation,  
932 hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if  
933 patients develop suicidal ideation or behavior, they should be urged to report these symptoms to  
934 their healthcare provider immediately.

935 **Suicidal Thoughts and Behaviors:** Instruct patients, their families, and/or their  
936 caregivers to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability,  
937 hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania,  
938 other unusual changes in behavior, worsening of depression, and suicidal ideation, especially  
939 early during antidepressant treatment and when the dose is adjusted up or down. Advise families  
940 and caregivers of patients to observe for the emergence of such symptoms on a day-to-day basis,  
941 since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or  
942 healthcare professional, especially if they are severe, abrupt in onset, or were not part of the  
943 patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk  
944 for suicidal thinking and behavior and indicate a need for very close monitoring and possibly  
945 changes in the medication.

946 **Severe Allergic Reactions:** Educate patients on the symptoms of hypersensitivity and  
947 to discontinue ZYBAN if they have a severe allergic reaction to ZYBAN.

948           **Seizure:** Instruct patients to discontinue ZYBAN and not restart it if they experience a  
949 seizure while on treatment. Advise patients that the excessive use or abrupt discontinuation of  
950 alcohol, benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of  
951 seizure. Advise patients to minimize or avoid use of alcohol.

952           **Angle-closure Glaucoma:** Patients should be advised that taking ZYBAN can cause  
953 mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure  
954 glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure  
955 glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is  
956 not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine  
957 whether they are susceptible to angle closure, and have a prophylactic procedure (e.g.,  
958 iridectomy), if they are susceptible [*see Warnings and Precautions (5.7)*].

959           **Bupropion-containing Products:** Educate patients that ZYBAN contains the same  
960 active ingredient (bupropion hydrochloride) found in WELLBUTRIN, WELLBUTRIN SR, and  
961 WELLBUTRIN XL, which are used to treat depression and that ZYBAN should not be used in  
962 conjunction with any other medications that contain bupropion (such as WELLBUTRIN, the  
963 immediate-release formulation; WELLBUTRIN SR, the sustained-release formulation;  
964 WELLBUTRIN XL or FORFIVO XL™, the extended-release formulations; and APLENZIN®,  
965 the extended-release formulation of bupropion hydrobromide). In addition, there are a number of  
966 generic bupropion HCl products for the immediate-, sustained-, and extended-release  
967 formulations.

968           **Potential for Cognitive and Motor Impairment:** Advise patients that any CNS-active  
969 drug like ZYBAN may impair their ability to perform tasks requiring judgment or motor and  
970 cognitive skills. Advise patients that until they are reasonably certain that ZYBAN does not  
971 adversely affect their performance, they should refrain from driving an automobile or operating  
972 complex, hazardous machinery. ZYBAN may lead to decreased alcohol tolerance.

973           **Concomitant Medications:** Counsel patients to notify their healthcare provider if they  
974 are taking or plan to take any prescription or over-the-counter drugs because ZYBAN and other  
975 drugs may affect each others' metabolisms.

976           **Pregnancy:** Advise patients to notify their healthcare provider if they become pregnant  
977 or intend to become pregnant during therapy.

978           **Precautions for Nursing Mothers:** Advise patients that ZYBAN is present in human  
979 milk in small amounts.

980           **Storage Information:** Instruct patients to store ZYBAN at room temperature, between  
981 59°F and 86°F (15°C to 30°C) and keep the tablets dry and out of the light.

982           **Administration Information:** Instruct patients to swallow ZYBAN Tablets whole so that  
983 the release rate is not altered. Do not chew, divide, or crush tablets; they are designed to slowly  
984 release drug in the body. When patients take more than 150 mg per day, instruct them to take  
985 ZYBAN in 2 doses at least 8 hours apart, to minimize the risk of seizures. Instruct patients if  
986 they miss a dose, not to take an extra tablet to make up for the missed dose and to take the next

987 tablet at the regular time because of the dose-related risk of seizure. ZYBAN can be taken with  
988 or without food. Advise patients that ZYBAN Tablets may have an odor.

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1001  
1002 ZYB:xPI  
1003

1004 **MEDICATION GUIDE**  
1005 **ZYBAN® (zi ban)**  
1006 **(bupropion hydrochloride)**  
1007 **Sustained-Release Tablets**

1008  
1009 Read this Medication Guide carefully before you start taking ZYBAN and each time  
1010 you get a refill. There may be new information. This information does not take the  
1011 place of talking with your healthcare provider about your medical condition or your  
1012 treatment. If you have any questions about ZYBAN, ask your healthcare provider or  
1013 pharmacist.

1014  
1015 **IMPORTANT: Be sure to read the three sections of this Medication Guide.**  
1016 **The first section is about the risk of changes in thinking and behavior,**  
1017 **depression and suicidal thoughts or actions with medicines used to quit**  
1018 **smoking; the second section is about the risk of suicidal thoughts and**  
1019 **actions with antidepressant medicines; and the third section is entitled**  
1020 **“What Other Important Information Should I Know About ZYBAN?”**

1021  
1022 **Quitting Smoking, Quit-Smoking Medications, Changes in Thinking and**  
1023 **Behavior, Depression, and Suicidal Thoughts or Actions**

1024

1025 This section of the Medication Guide is only about the risk of changes in thinking  
1026 and behavior, depression and suicidal thoughts or actions with drugs used to quit  
1027 smoking. Talk to your healthcare provider or your family member's healthcare  
1028 provider about:

- 1029 • all risks and benefits of quit-smoking medicines.
- 1030 • all treatment choices for quitting smoking.

1031

1032 Some people have had changes in behavior, hostility, agitation, depression, suicidal  
1033 thoughts or actions while taking ZYBAN to help them quit smoking. These  
1034 symptoms can develop during treatment with ZYBAN or after stopping treatment  
1035 with ZYBAN.

1036

1037 If you, your family member, or your caregiver notice agitation, hostility,  
1038 depression, or changes in thinking or behavior that are not typical for you, or you  
1039 have any of the following symptoms, stop taking ZYBAN and call your healthcare  
1040 provider right away:

1041

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

1042

1043 When you try to quit smoking, with or without ZYBAN, you may have symptoms  
1044 that may be due to nicotine withdrawal, including urge to smoke, depressed mood,  
1045 trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty  
1046 concentrating, restlessness, decreased heart rate, and increased appetite or weight  
1047 gain. Some people have even experienced suicidal thoughts when trying to quit  
1048 smoking without medication. Sometimes quitting smoking can lead to worsening of  
1049 mental health problems that you already have, such as depression.

1050

1051 Before taking ZYBAN, tell your healthcare provider if you have ever had depression  
1052 or other mental illnesses. You should also tell your healthcare provider about any  
1053 symptoms you had during other times you tried to quit smoking, with or without  
1054 ZYBAN.

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

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

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines.

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

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

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

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

1092 **What else do I need to know about antidepressant medicines?**

1093 • **Never stop an antidepressant medicine without first talking to a**  
 1094 **healthcare provider.** Stopping an antidepressant medicine suddenly can cause  
 1095 other symptoms.

1096 • **Antidepressants are medicines used to treat depression and other**  
 1097 **illnesses.** It is important to discuss all the risks of treating depression and also  
 1098 the risks of not treating it. Patients and their families or other caregivers should  
 1099 discuss all treatment choices with the healthcare provider, not just the use of  
 1100 antidepressants.

1101 • **Antidepressant medicines have other side effects.** Talk to the healthcare  
 1102 provider about the side effects of the medicine prescribed for you or your family  
 1103 member.

1104 • **Antidepressant medicines can interact with other medicines.** Know all of  
 1105 the medicines that you or your family member takes. Keep a list of all medicines  
 1106 to show the healthcare provider. Do not start new medicines without first  
 1107 checking with your healthcare provider.

1108  
 1109 It is not known if ZYBAN is safe and effective in children under the age of 18.

1110  
 1111 **What other important information should I know about ZYBAN?**

- 1112 • **Seizures: There is a chance of having a seizure (convulsion, fit) with**  
 1113 **ZYBAN, especially in people:**
- with certain medical problems.
  - who take certain medicines.

1114  
 1115  
 1116  
 1117 The chance of having seizures increases with higher doses of ZYBAN. For more  
 1118 information, see the sections “Who should not take ZYBAN?” and “What should I  
 1119 tell my healthcare provider before taking ZYBAN?” Tell your healthcare provider  
 1120 about all of your medical conditions and all the medicines you take. **Do not**  
 1121 **take any other medicines while you are taking ZYBAN unless your**  
 1122 **healthcare provider has said it is okay to take them.**

1124 **If you have a seizure while taking ZYBAN, stop taking the tablets and**  
1125 **call your healthcare provider right away.** Do not take ZYBAN again if you  
1126 have a seizure.

1127  
1128 • **High blood pressure (hypertension).** Some people get high blood  
1129 **pressure that can be severe, while taking ZYBAN.** The chance of high blood  
1130 pressure may be higher if you also use nicotine replacement therapy (such as a  
1131 nicotine patch) to help you stop smoking (see the section of this Medication  
1132 Guide called “How should I take ZYBAN?”).

1133 • **Manic episodes.** Some people may have periods of mania while taking ZYBAN,  
1134 including:

- 1135 • Greatly increased energy
- 1136 • Severe trouble sleeping
- 1137 • Racing thoughts
- 1138 • Reckless behavior
- 1139 • Unusually grand ideas
- 1140 • Excessive happiness or irritability
- 1141 • Talking more or faster than usual

1142 If you have any of the above symptoms of mania, call your healthcare provider.

1143 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or  
1144 behaviors while taking ZYBAN, including delusions (believe you are someone  
1145 else), hallucinations (seeing or hearing things that are not there), paranoia  
1146 (feeling that people are against you), or feeling confused. If this happens to you,  
1147 call your healthcare provider.

1148 • **Visual problems.**

- 1149 • eye pain
- 1150 • changes in vision
- 1151 • swelling or redness in or around the eye

1152 Only some people are at risk for these problems. You may want to undergo an  
1153 eye examination to see if you are at risk and receive preventative treatment if  
1154 you are.

1155 • **Severe allergic reactions.** Some people can have severe allergic  
1156 **reactions to ZYBAN. Stop taking ZYBAN and call your healthcare**  
1157 **provider right away** if you get a rash, itching, hives, fever, swollen lymph  
1158 glands, painful sores in the mouth or around the eyes, swelling of the lips or  
1159 tongue, chest pain, or have trouble breathing. These could be signs of a serious  
1160 allergic reaction.

1161  
1162 **What is ZYBAN?**

1163 ZYBAN is a prescription medicine to help people quit smoking.

1164  
1165 ZYBAN should be used with a patient support program. It is important to participate  
1166 in the behavioral program, counseling, or other support program your healthcare  
1167 professional recommends.

1168  
1169 Quitting smoking can lower your chances of having lung disease, heart disease, or  
1170 getting certain types of cancer that are related to smoking.

1171  
1172 **Who should not take ZYBAN?**

1173 **Do not take ZYBAN if you:**

- 1174 • have or had a seizure disorder or epilepsy.
- 1175 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1176 • **are taking any other medicines that contain bupropion, including**  
1177 **WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, APLENZIN<sup>®</sup>, or**  
1178 **FORFIVO XL<sup>™</sup>.** Bupropion is the same active ingredient that is in ZYBAN.
- 1179 • drink a lot of alcohol and abruptly stop drinking, or take medicines called  
1180 sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines,  
1181 and you stop taking them all of a sudden.
- 1182 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or  
1183 pharmacist if you are not sure if you take an MAOI, including the antibiotic  
1184 linezolid.
  - 1185 • **do not take an MAOI within 2 weeks of stopping ZYBAN unless**  
1186 **directed to do so by your healthcare provider.**
  - 1187 • **do not start ZYBAN if you stopped taking an MAOI in the last 2 weeks**  
1188 **unless directed to do so by your healthcare provider.**
- 1189 • are allergic to the active ingredient in ZYBAN, bupropion, or to any of the  
1190 inactive ingredients. See the end of this Medication Guide for a complete list of  
1191 ingredients in ZYBAN.

1192  
1193 **What should I tell my healthcare provider before taking ZYBAN?**

1194 Tell your healthcare provider if you have ever had depression, suicidal thoughts or  
1195 actions, or other mental health problems. You should also tell your healthcare  
1196 provider about any symptoms you had during other times you tried to quit  
1197 smoking, with or without ZYBAN. See “Quitting Smoking, Quit-Smoking  
1198 Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts  
1199 or Actions.”

- 1200  
1201 • **Tell your healthcare provider about your other medical conditions,**  
1202 **including if you:**
  - 1203 • have liver problems, especially cirrhosis of the liver.

- 1204 • have kidney problems.
- 1205 • have, or have had, an eating disorder such as anorexia nervosa or bulimia.
- 1206 • have had a head injury.
- 1207 • have had a seizure (convulsion, fit).
- 1208 • have a tumor in your nervous system (brain or spine).
- 1209 • have had a heart attack, heart problems, or high blood pressure.
- 1210 • are a diabetic taking insulin or other medicines to control your blood sugar.
- 1211 • drink alcohol.
- 1212 • abuse prescription medicines or street drugs.
- 1213 • are pregnant or plan to become pregnant.
- 1214 • are breastfeeding. ZYBAN passes into your milk in small amounts
- 1215 • **Tell your healthcare provider about all the medicines you take**, including
- 1216 prescription, over-the-counter medicines, vitamins, and herbal supplements.
- 1217 Many medicines increase your chances of having seizures or other serious side
- 1218 effects if you take them while you are taking ZYBAN.
- 1219

1220 **How should I take ZYBAN?**

- 1221 • Start ZYBAN before you stop smoking to give ZYBAN time to build up in your
- 1222 body. It takes about 1 week for ZYBAN to start working.
- 1223 • Pick a date to stop smoking that is during the second week you are taking
- 1224 ZYBAN.
- 1225 • Take ZYBAN exactly as prescribed by your healthcare provider. Do not change
- 1226 your dose or stop taking ZYBAN without talking with your healthcare provider
- 1227 first.
- 1228 • ZYBAN is usually taken for 7 to 12 weeks. Your healthcare provider may decide
- 1229 to prescribe ZYBAN for longer than 12 weeks to help you stop smoking. Follow
- 1230 your healthcare provider's instructions.
- 1231 • **Swallow ZYBAN Tablets whole. Do not chew, cut, or crush ZYBAN**
- 1232 **Tablets.** If you do, the medicine will be released into your body too quickly. If
- 1233 this happens you may be more likely to get side effects including seizures. **Tell**
- 1234 **your healthcare provider if you cannot swallow tablets.**
- 1235 • ZYBAN Tablets may have an odor. This is normal.
- 1236 • Take your doses of ZYBAN at least 8 hours apart.
- 1237 • You may take ZYBAN with or without food.
- 1238 • It is not dangerous to smoke and take ZYBAN at the same time. But, you will
- 1239 lower your chance of breaking your smoking habit if you smoke after the date
- 1240 you set to stop smoking.
- 1241 • You may use ZYBAN and nicotine patches (a type of nicotine replacement
- 1242 therapy) at the same time, following the precautions below.

- 1243 • You should only use ZYBAN and nicotine patches together under the care of  
1244 your healthcare provider. Using ZYBAN and nicotine patches together may  
1245 raise your blood pressure, and sometimes this can be severe.  
1246 • Tell your healthcare provider if you plan to use nicotine patches. Your  
1247 healthcare provider should check your blood pressure regularly if you use  
1248 nicotine patches with ZYBAN to help you quit smoking.  
1249 • If you miss a dose, do not take an extra dose to make up for the dose you  
1250 missed. Wait and take your next dose at the regular time. **This is very**  
1251 **important.** Too much ZYBAN can increase your chance of having a seizure.  
1252 • If you take too much ZYBAN, or overdose, call your local emergency room or  
1253 poison control center right away.

1254 **Do not take any other medicines while taking ZYBAN unless your**  
1255 **healthcare provider has told you it is okay.**

#### 1256 **What should I avoid while taking ZYBAN?**

- 1257 • Limit or avoid using alcohol during treatment with ZYBAN. If you usually drink a  
1258 lot of alcohol, talk with your healthcare provider before suddenly stopping. If  
1259 you suddenly stop drinking alcohol, you may increase your chance of having  
1260 seizures.  
1261 • Do not drive a car or use heavy machinery until you know how ZYBAN affects  
1262 you. ZYBAN can affect your ability to do these things safely.  
1263  
1264

#### 1265 **What are possible side effects of ZYBAN?**

1266 ZYBAN can cause serious side effects. See the sections at the beginning of this  
1267 Medication Guide for information about serious side effects of ZYBAN.  
1268

1269 The most common side effects of ZYBAN include:

- 1270 • trouble sleeping  
1271 • stuffy nose  
1272 • dry mouth  
1273 • dizziness  
1274 • feeling anxious  
1275 • nausea  
1276 • constipation  
1277 • joint aches

1278 If you have trouble sleeping, do not take ZYBAN too close to bedtime.  
1279

1280 Tell your healthcare provider right away about any side effects that bother you.  
1281

1282 These are not all the possible side effects of ZYBAN. For more information, ask your  
1283 healthcare provider or pharmacist.

1284

1285 Call your doctor for medical advice about side effects. You may report side effects  
1286 to FDA at 1-800-FDA-1088.

1287

1288 You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

1289

### 1290 **How should I store ZYBAN?**

1291 • Store ZYBAN at room temperature between 59°F and 86°F (15°C to 30°C).

1292 • Keep ZYBAN dry and out of the light.

1293

1294 **Keep ZYBAN and all medicines out of the reach of children.**

1295

### 1296 **General information about ZYBAN**

1297 Medicines are sometimes prescribed for purposes other than those listed in a  
1298 Medication Guide. Do not use ZYBAN for a condition for which it was not prescribed.

1299 Do not give ZYBAN to other people, even if they have the same symptoms you  
1300 have. It may harm them.

1301

1302 If you take a urine drug screening test, ZYBAN may make the test result positive  
1303 for amphetamines. If you tell the person giving you the drug screening test that  
1304 you are taking ZYBAN, they can do a more specific drug screening test that should  
1305 not have this problem.

1306

1307 This Medication Guide summarizes important information about ZYBAN. If you  
1308 would like more information, talk with your healthcare provider. You can ask your  
1309 healthcare provider or pharmacist for information about ZYBAN that is written for  
1310 health professionals.

1311

1312 For more information about ZYBAN, call 1-888-825-5249.

1313

### 1314 **What are the ingredients in ZYBAN?**

1315 Active ingredient: bupropion hydrochloride.

1316

1317 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose,  
1318 magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80  
1319 and titanium dioxide. The tablets are printed with edible black ink. In addition, the  
1320 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

1321

1322 This Medication Guide has been approved by the U.S. Food and Drug  
1323 Administration.  
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