

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)

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.

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: 6/2016

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1 FULL PRESCRIBING INFORMATION

WARNING: NEUROPSYCHIATRIC REACTIONS; AND SUICIDAL THOUGHTS AND BEHAVIORS

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

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

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

SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

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

1 INDICATIONS AND USAGE

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 the**
33 **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

37 To minimize the risk of seizure:

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

42 ZYBAN should be swallowed whole and not crushed, divided, or chewed, as this may lead to an
43 increased risk of adverse effects including seizures [*see Warnings and Precautions (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 but
51 consider whether the patient may benefit from ongoing treatment. Patients who successfully quit
52 after 12 weeks of treatment but do not feel ready to discontinue treatment should be considered
53 for ongoing therapy with ZYBAN; longer treatment should be guided by the relative benefits and
54 risks for individual patients.

55 It is important that patients continue to receive counseling and support throughout treatment with
56 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 and
59 receive support from their physicians or other healthcare professionals. It is important to ensure
60 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 improve
66 their chances for success on subsequent attempts. Patients who are unsuccessful should be
67 evaluated to determine why they failed. A new quit attempt should be encouraged when factors
68 that contributed to failure can be eliminated or reduced, and conditions are more favorable.

69 **2.4 Maintenance**

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

73 **2.5 Combination Treatment with ZYBAN and a Nicotine Transdermal System** 74 **(NTS)**

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

79 **2.6 Dose Adjustment in Patients with Hepatic Impairment**

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

84 **2.7 Dose Adjustment in Patients with Renal Impairment**

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

88 **2.8 Use of ZYBAN with Reversible MAOIs Such as Linezolid or Methylene Blue**

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

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

99 Therapy with ZYBAN may be resumed 24 hours after the last dose of linezolid or intravenous
100 methylene blue.

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

105 **3 DOSAGE FORMS AND STRENGTHS**

106 150 mg – purple, round, biconvex, film-coated, sustained-release tablets printed with “ZYBAN
107 150”.

108 **4 CONTRAINDICATIONS**

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

126 **5 WARNINGS AND PRECAUTIONS**

127 **5.1 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation** 128 **Treatment**

129 Serious neuropsychiatric symptoms have been reported in patients taking ZYBAN for smoking
130 cessation. These have included changes in mood (including depression and mania), psychosis,
131 hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety,
132 and panic, as well as suicidal ideation, suicide attempt, and completed suicide [see *Boxed*

133 *Warning, Adverse Reactions (6.2)]*. Observe patients for the occurrence of neuropsychiatric
134 reactions. Instruct patients to contact a healthcare professional if such reactions occur.

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

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

142 **5.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young** 143 **Adults**

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

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

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

169 **Table 1. Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled**
 170 **Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Subjects Treated
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

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

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

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

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

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

192 **Families and caregivers of patients being treated with antidepressants for MDD or other**
 193 **indications, both psychiatric and nonpsychiatric, should be alerted about the need to**
 194 **monitor patients for the emergence of agitation, irritability, unusual changes in behavior,**
 195 **and the other symptoms described above, as well as the emergence of suicidality, and to**
 196 **report such symptoms immediately to healthcare providers. Such monitoring should**

197 **include daily observation by families and caregivers. Prescriptions for ZYBAN should be**
198 **written for the smallest quantity of tablets consistent with good patient management, in**
199 **order to reduce the risk of overdose.**

200 **5.3 Seizure**

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

204 The risk of seizures is also related to patient factors, clinical situations, and concomitant
205 medications that lower the seizure threshold. Consider these risks before initiating treatment with
206 ZYBAN. ZYBAN is contraindicated in patients with a seizure disorder, current or prior
207 diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol,
208 benzodiazepines, barbiturates, and antiepileptic drugs [*see Contraindications (4), Drug*
209 *Interactions (7.3)*]. The following conditions can also increase the risk of seizure: severe head
210 injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant
211 use of other medications that lower the seizure threshold (e.g., other bupropion products,
212 antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic
213 disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), use of
214 illicit drugs (e.g., cocaine), or abuse or misuse of prescription drugs such as CNS stimulants.
215 Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic
216 drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines,
217 sedative/hypnotics, or opiates.

218 Incidence of Seizure with Bupropion Use

219 Doses for smoking cessation should not exceed 300 mg per day. The seizure rate associated with
220 doses of sustained-release bupropion in depressed patients up to 300 mg per day is
221 approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1000) at doses up to
222 400 mg per day.

223 The risk of seizure can be reduced if the dose of ZYBAN for smoking cessation does not exceed
224 300 mg per day, given as 150 mg twice daily, and titration rate is gradual.

225 **5.4 Hypertension**

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

230 Data from a comparative trial of ZYBAN, nicotine transdermal system (NTS), the combination
231 of ZYBAN plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of
232 treatment-emergent hypertension in patients treated with the combination of ZYBAN and NTS.
233 In this trial, 6.1% of subjects treated with the combination of ZYBAN and NTS had

234 treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with
235 ZYBAN, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-
236 existing hypertension. Three subjects (1.2%) treated with the combination of ZYBAN and NTS
237 and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension
238 compared with none of the subjects treated with ZYBAN or placebo. Monitoring of blood
239 pressure is recommended in patients who receive the combination of bupropion and nicotine
240 replacement.

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

246 **5.5 Activation of Mania/Hypomania**

247 Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears
248 to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder.
249 There were no reports of activation of psychosis or mania in clinical trials with ZYBAN
250 conducted in nondepressed smokers. Bupropion is not approved for use in treating bipolar
251 depression.

252 **5.6 Psychosis and Other Neuropsychiatric Reactions**

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

258 In clinical trials with ZYBAN conducted in nondepressed smokers, the incidence of
259 neuropsychiatric side effects was generally comparable to placebo. However, in the
260 postmarketing experience, patients taking ZYBAN to quit smoking have reported similar types
261 of neuropsychiatric symptoms to those reported by patients in the clinical trials of bupropion for
262 depression.

263 **5.7 Angle-Closure Glaucoma**

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

267 **5.8 Hypersensitivity Reactions**

268 Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion.
269 Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring

270 medical treatment. In addition, there have been rare, spontaneous postmarketing reports of
271 erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with
272 bupropion. Instruct patients to discontinue ZYBAN and consult a healthcare provider if they
273 develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest
274 pain, edema, and shortness of breath) during treatment.

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

277 **6 ADVERSE REACTIONS**

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

- 279 • Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [*see Boxed*
280 *Warning, Warnings and Precautions (5.1)*]
- 281 • Suicidal thoughts and behaviors in adolescents and young adults [*see Boxed Warning,*
282 *Warnings and Precautions (5.2)*]
- 283 • Seizure [*see Warnings and Precautions (5.3)*]
- 284 • Hypertension [*see Warnings and Precautions (5.4)*]
- 285 • Activation of mania or hypomania [*see Warnings and Precautions (5.5)*]
- 286 • Psychosis and other neuropsychiatric reactions [*see Warnings and Precautions (5.6)*]
- 287 • Angle-closure glaucoma [*see Warnings and Precautions (5.7)*]
- 288 • Hypersensitivity reactions [*see Warnings and Precautions (5.8)*]

289 **6.1 Clinical Trials Experience**

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

293 Adverse Reactions Leading to Discontinuation of Treatment

294 Adverse reactions were sufficiently troublesome to cause discontinuation of treatment in 8% of
295 the 706 subjects treated with ZYBAN and 5% of the 313 patients treated with placebo. The more
296 common events leading to discontinuation of treatment with ZYBAN included nervous system
297 disturbances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

298 Commonly Observed Adverse Reactions

299 The most commonly observed adverse reactions consistently associated with the use of ZYBAN
300 were dry mouth and insomnia. The incidence of dry mouth and insomnia may be related to the
301 dose of ZYBAN. The occurrence of these adverse reactions may be minimized by reducing the
302 dose of ZYBAN. In addition, insomnia may be minimized by avoiding bedtime doses.

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

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

Adverse Reaction	ZYBAN 100 to 300 mg/day (n = 461) %	Placebo (n = 150) %
Body (General)		
Neck pain	2	<1
Allergic reaction	1	0
Cardiovascular		
Hot flashes	1	0
Hypertension	1	<1
Digestive		
Dry mouth	11	5
Increased appetite	2	<1
Anorexia	1	<1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous system		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1
Thinking abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	<1
Rash	3	<1
Dry skin	2	0
Urticaria	1	0
Special senses		
Taste perversion	2	<1

308

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

Adverse Experience (COSTART Term)	ZYBAN 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	<1	1	3	1
Neck pain	2	1	<1	0
Facial edema	<1	0	1	0
Cardiovascular				
Hypertension	1	<1	2	0
Palpitations	2	0	1	0
Digestive				
Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	<1	<1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous system				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	<1	2	2
Tremor	1	<1	2	0
Dysphoria	<1	1	2	1
Respiratory				

Rhinitis	12	11	9	8
Increased cough	3	5	<1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction ^a	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

311 ^a Subjects randomized to ZYBAN or placebo received placebo patches.

312 Adverse reactions in a 1-year maintenance trial and a 12-week COPD trial with ZYBAN were
313 quantitatively and qualitatively similar to those observed in the dose-response and comparator
314 trials.

315 Other Adverse Reactions Observed during the Clinical Development of Bupropion

316 In addition to the adverse reactions noted above, the following adverse reactions have been
317 reported in clinical trials with the sustained-release formulation of bupropion in depressed
318 subjects and in nondepressed smokers, as well as in clinical trials with the immediate-release
319 formulation of bupropion.

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

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

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

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

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

340 *Hemic and Lymphatic*: Infrequent was ecchymosis.

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

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

343 *Nervous System*: Frequent were agitation, depression, and irritability. Infrequent were
344 abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory,
345 depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia,
346 paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and
347 hypomania.

348 *Respiratory*: Rare was bronchospasm.

349 *Skin*: Frequent was sweating.

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

352 *Urogenital*: Frequent was urinary frequency. Infrequent were impotence, polyuria, and urinary
353 urgency.

354 **6.2 Postmarketing Experience**

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

359 Body (General)

360 Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed
361 hypersensitivity. These symptoms may resemble serum sickness [see *Warnings and Precautions*
362 (5.8)].

363 Cardiovascular

364 Cardiovascular disorder, complete AV block, extrasystoles, hypotension, myocardial infarction,
365 phlebitis, and pulmonary embolism.

366 Digestive

367 Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased
368 salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool
369 abnormality.

370 Endocrine

371 Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

372 Hemic and Lymphatic

373 Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.

374 Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications,
375 were observed when bupropion was coadministered with warfarin.

376 Metabolic and Nutritional

377 Glycosuria.

378 Musculoskeletal

379 Arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.

380 Nervous System

381 Abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, completed suicide,
382 delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome (dyskinesia, dystonia,
383 hypokinesia, parkinsonism), hallucinations, increased libido, manic reaction, neuralgia,
384 neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

385 Respiratory

386 Pneumonia.

387 Skin

388 Alopecia, angioedema, exfoliative dermatitis, hirsutism, and Stevens-Johnson syndrome.

389 Special Senses

390 Deafness, increased intraocular pressure, and mydriasis.

391 Urogenital

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

395 7 DRUG INTERACTIONS

396 7.1 Potential for Other Drugs to Affect ZYBAN

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

400 Inhibitors of CYP2B6

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

405 Inducers of CYP2B6

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

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

415 7.2 Potential for ZYBAN to Affect Other Drugs

416 Drugs Metabolized by CYP2D6

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

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

430 **7.3 Drugs that Lower Seizure Threshold**

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

435 **7.4 Dopaminergic Drugs (Levodopa and Amantadine)**

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

441 **7.5 Use with Alcohol**

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

445 **7.6 MAO Inhibitors**

446 Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs
447 and bupropion is contraindicated because there is an increased risk of hypertensive reactions if
448 bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute
449 toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days should
450 elapse between discontinuation of an MAOI and initiation of treatment with ZYBAN.
451 Conversely, at least 14 days should be allowed after stopping ZYBAN before starting an MAOI
452 intended to treat psychiatric disorders [*see Dosage and Administration (2.8), Contraindications*
453 *(4)*].

454 **7.7 Smoking Cessation**

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

458 **7.8 Drug-Laboratory Test Interactions**

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

464 **8 USE IN SPECIFIC POPULATIONS**

465 **8.1 Pregnancy**

466 Pregnancy Category C.

467 Risk Summary

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

477 Clinical Considerations

478 Pregnant smokers should be encouraged to attempt cessation using educational and behavioral
479 interventions before pharmacological approaches are used.

480 Human Data

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

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

494 Study findings on bupropion exposure during the first trimester and risk for left ventricular
495 outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a
496 possible association. The United Healthcare database lacked sufficient power to evaluate this
497 association; the NBDPS found increased risk for LVOTO (n = 10; adjusted OR = 2.6; 95% CI:
498 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

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

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

509 Animal Data

510 In studies conducted in rats and rabbits, bupropion was administered orally during the period of
511 organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 15
512 and 10 times the MRHD respectively, on a mg per m² basis). No clear evidence of teratogenic
513 activity was found in either species; however, in rabbits, slightly increased incidences of fetal
514 malformations and skeletal variations were observed at the lowest dose tested (25 mg per kg per
515 day, approximately 2 times the MRHD on a mg per m² basis) and greater. Decreased fetal
516 weights were observed at 50 mg per kg and greater.

517 When rats were administered bupropion at oral doses of up to 300 mg per kg per day
518 (approximately 10 times the MRHD on a mg per m² basis) prior to mating and throughout
519 pregnancy and lactation, there were no apparent adverse effects on offspring development.

520 **8.3 Nursing Mothers**

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

526 **8.4 Pediatric Use**

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

529 **8.5 Geriatric Use**

530 Of the approximately 6,000 subjects who participated in clinical trials with bupropion
531 sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥65 years and
532 47 were aged ≥75 years. In addition, several hundred subjects aged ≥65 years participated in
533 clinical trials using the immediate-release formulation of bupropion (depression trials). No
534 overall differences in safety or effectiveness were observed between these subjects and younger

535 subjects. Reported clinical experience has not identified differences in responses between the
536 elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled
537 out.

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

544 **8.6 Renal Impairment**

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

550 **8.7 Hepatic Impairment**

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

555 **9 DRUG ABUSE AND DEPENDENCE**

556 **9.1 Controlled Substance**

557 Bupropion is not a controlled substance.

558 **9.2 Abuse**

559 Humans

560 Controlled clinical trials conducted in normal volunteers, in subjects with a history of multiple
561 drug abuse, and in depressed subjects showed some increase in motor activity and
562 agitation/excitement, often typical of central stimulant activity.

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

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

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

578 Animals

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

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

588 **10 OVERDOSAGE**

589 **10.1 Human Overdose Experience**

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

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

600 **10.2 Overdosage Management**

601 Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone
602 numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR).
603 Call 1-800-222-1222 or refer to www.poison.org.

635 12.3 Pharmacokinetics

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

640 Absorption

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

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

647 ZYBAN can be taken with or without food. Bupropion C_{\max} and AUC were increased by 11% to
648 35%, and 16% to 19%, respectively, when ZYBAN was administered with food to healthy
649 volunteers in three trials. The food effect is not considered clinically significant.

650 Distribution

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

655 Metabolism

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

669 Following a single-dose administration of ZYBAN in humans, C_{\max} of hydroxybupropion occurs
670 approximately 6 hours post-dose and is approximately 10 times the peak level of the parent drug

671 at steady state. The elimination half-life of hydroxybupropion is approximately 20 (\pm 5) hours
672 and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations
673 for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the
674 hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (\pm 10) and
675 37 (\pm 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion,
676 respectively.

677 Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 to
678 450 mg per day.

679 Elimination

680 Following oral administration of 200 mg of 14 C-bupropion in humans, 87% and 10% of the
681 radioactive dose were recovered in the urine and feces, respectively. Only 0.5% of the oral dose
682 was excreted as unchanged bupropion.

683 Population Subgroups

684 Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure
685 [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the
686 degree and extent of accumulation of the active metabolites of bupropion. The elimination of the
687 major metabolites of bupropion may be affected by reduced renal or hepatic function because
688 they are moderately polar compounds and are likely to undergo further metabolism or
689 conjugation in the liver prior to urinary excretion.

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

705 *Hepatic Impairment:* The effect of hepatic impairment on the pharmacokinetics of bupropion
706 was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease and one in
707 subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of

708 hydroxybupropion was significantly longer in 8 subjects with alcoholic liver disease than in
 709 8 healthy volunteers (32 ± 14 hours versus 21 ± 5 hours, respectively). Although not statistically
 710 significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be
 711 greater (by 53% to 57%) in volunteers with alcoholic liver disease. The differences in half-life
 712 for bupropion and the other metabolites in the 2 groups were minimal.

713 The second trial demonstrated no statistically significant differences in the pharmacokinetics of
 714 bupropion and its active metabolites in 9 subjects with mild-to-moderate hepatic cirrhosis
 715 compared with 8 healthy volunteers. However, more variability was observed in some of the
 716 pharmacokinetic parameters for bupropion (AUC , C_{max} , and T_{max}) and its active metabolites ($t_{1/2}$)
 717 in subjects with mild-to-moderate hepatic cirrhosis. In 8 subjects with severe hepatic cirrhosis,
 718 significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table
 719 4).

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

	C_{max}	AUC	$t_{1/2}$	T_{max}^a
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

722 ^a = Difference.

723 **Smokers:** The effects of cigarette smoking on the pharmacokinetics of bupropion were studied
 724 in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were
 725 nonsmokers. Following oral administration of a single 150-mg dose of ZYBAN, there were no
 726 statistically significant differences in C_{max} , half-life, T_{max} , AUC, or clearance of bupropion or its
 727 major metabolites between smokers and nonsmokers.

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

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

736 **Age:** The effects of age on the pharmacokinetics of bupropion and its metabolites have not been
 737 fully characterized, but an exploration of steady-state bupropion concentrations from several
 738 depression efficacy trials involving subjects dosed in a range of 300 to 750 mg per day, on a 3-
 739 times-daily schedule, revealed no relationship between age (18 to 83 years) and plasma
 740 concentration of bupropion. A single-dose pharmacokinetic trial demonstrated that the

741 disposition of bupropion and its metabolites in elderly subjects was similar to that of younger
742 subjects. These data suggest there is no prominent effect of age on bupropion concentration;
743 however, another single- and multiple-dose pharmacokinetics trial suggested that the elderly are
744 at increased risk for accumulation of bupropion and its metabolites [*see Use in Specific*
745 *Populations (8.5)*].

746 **Gender:** Pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90
747 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations
748 of bupropion. The mean systemic exposure (AUC) was approximately 13% higher in male
749 volunteers compared with female volunteers. The clinical significance of this finding is
750 unknown.

751 Drug Interactions

752 **Potential for Other Drugs to Affect ZYBAN:** In vitro studies indicate that bupropion is
753 primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug
754 interactions between ZYBAN and drugs that are inhibitors or inducers of CYP2B6. In addition,
755 in vitro studies suggest that paroxetine, sertraline, norfluoxetine, fluvoxamine, and nelfinavir
756 inhibit the hydroxylation of bupropion.

757 **Inhibitors of CYP2B6: Ticlopidine, Clopidogrel:** In a trial in healthy male volunteers,
758 clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (C_{max} and
759 AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine,
760 respectively. The exposures (C_{max} and AUC) of hydroxybupropion were decreased 50% and
761 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This effect is
762 thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

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

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

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

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

778 In a second healthy volunteer trial, ritonavir at a dose of 600 mg twice daily decreased the AUC
779 and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the
780 hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by
781 50%, and the erythrohydrobupropion decreased by 68%.

782 In another healthy volunteer trial, lopinavir 400 mg/ritonavir 100 mg twice daily decreased
783 bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by
784 50% and 31%, respectively.

785 *Efavirenz*: In a trial in healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the
786 AUC and C_{max} of bupropion by approximately 55% and 34%, respectively. The AUC of
787 hydroxybupropion was unchanged, whereas C_{max} of hydroxybupropion was increased by 50%.

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

790 Potential for ZYBAN to Affect Other Drugs

791 Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in
792 humans. In one trial, following chronic administration of bupropion 100 mg three times daily to
793 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism.
794 Nevertheless, there may be potential for clinically important alterations of blood levels of co-
795 administered drugs.

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

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

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

808 **13 NONCLINICAL TOXICOLOGY**

809 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

810 Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up to 300
811 and 150 mg per kg per day, respectively. These doses are approximately 10 and 2 times the
812 MRHD, respectively, on a mg per m² basis. In the rat study there was an increase in nodular
813 proliferative lesions of the liver at doses of 100 to 300 mg per kg per day (approximately 3 to 10

814 times the MRHD on a mg per m² basis); lower doses were not tested. The question of whether or
815 not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar
816 liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver
817 and other organs was seen in either study.

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

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

823 **14 CLINICAL STUDIES**

824 The efficacy of ZYBAN as an aid to smoking cessation was demonstrated in
825 3 placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1,940,
826 greater than or equal to 15 cigarettes per day). In these trials, ZYBAN was used in conjunction
827 with individual smoking cessation counseling.

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

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

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

843 **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% ^a (20-35)	36% ^a (28-43)
Week 12	14% (8-19)	20% (13-26)	20% (14-27)	25% ^a (18-32)
Week 26	11% (6-16)	16% (11-22)	18% (12-24)	19% ^a (13-25)

844 ^a Significantly different from placebo ($P \leq 0.05$).

845 The second trial was a comparator trial conducted at 4 clinical centers. Four treatments were
 846 evaluated: ZYBAN 300 mg per day, nicotine transdermal system (NTS) 21 mg per day,
 847 combination of ZYBAN 300 mg per day plus NTS 21 mg per day, and placebo. Subjects were
 848 treated for 9 weeks. Treatment with ZYBAN was initiated at 150 mg per day while the subject
 849 was still smoking and was increased after 3 days to 300 mg per day given as 150 mg twice daily.
 850 NTS 21 mg per day was added to treatment with ZYBAN after approximately 1 week when the
 851 subject reached the target quit date. During Weeks 8 and 9 of the trial, NTS was tapered to 14
 852 and 7 mg per day, respectively. Quitting, defined as total abstinence during Weeks 4 through 7,
 853 was determined by subject daily diaries and verified by expired air carbon monoxide levels. In
 854 this trial, subjects treated with any of the 3 treatments achieved greater 4-week abstinence rates
 855 than subjects treated with placebo.

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

857 **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)

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 been
 869 replicated, and, therefore should not be interpreted as demonstrating the superiority of any of the
 870 active treatment arms over any other.

871 The third trial was a long-term maintenance trial conducted at 5 clinical centers. Subjects in this
 872 trial received open-label ZYBAN 300 mg per day for 7 weeks. Subjects who quit smoking while
 873 receiving ZYBAN (n = 432) were then randomized to ZYBAN 300 mg per day or placebo for a
 874 total trial duration of 1 year. Abstinence from smoking was determined by subject self-report and
 875 verified by expired air carbon monoxide levels. This trial demonstrated that at 6 months,
 876 continuous abstinence rates were significantly higher for subjects continuing to receive ZYBAN
 877 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 unselected
 879 population may be lower than the above rates. Quit rates for ZYBAN were similar in subjects
 880 with and without prior quit attempts using nicotine replacement therapy.

881 Treatment with ZYBAN reduced withdrawal symptoms compared with placebo. Reductions on
 882 the following withdrawal symptoms were most pronounced: irritability, frustration, or anger;

883 anxiety; difficulty concentrating; restlessness; and depressed mood or negative affect. Depending
 884 on the trial and the measure used, treatment with ZYBAN showed evidence of reduction in
 885 craving for cigarettes or urge to smoke compared with placebo.

886 **Use in Patients with Chronic Obstructive Pulmonary Disease (COPD)**

887 ZYBAN was evaluated in a randomized, double-blind, comparator trial of 404 subjects with
 888 mild-to-moderate COPD defined as FEV₁ greater than or equal to 35%, FEV₁/FVC less than or
 889 equal to 70%, and a diagnosis of chronic bronchitis, emphysema, and/or small airways disease.
 890 Subjects aged 36 to 76 years were randomized to ZYBAN 300 mg per day (n = 204) or placebo
 891 (n = 200) and treated for 12 weeks. Treatment with ZYBAN was initiated at 150 mg per day for
 892 3 days 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 **Table 7. COPD Trial: Quit Rates by Treatment Group**

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

897 ^a Significantly different from placebo (P<0.05).

898 **16 HOW SUPPLIED/STORAGE AND HANDLING**

899 ZYBAN sustained-release tablets, 150 mg of bupropion hydrochloride, are purple, round,
 900 biconvex, film-coated tablets printed with “ZYBAN 150” in bottles of 60 (NDC 0173-0556-02)
 901 tablets and the ZYBAN Advantage Pack[®] containing 1 bottle of 60 (NDC 0173-0556-01) tablets.

902 Store at room temperature, 20° to 25°C (68° to 77°F); excursions permitted between 15°C and
 903 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from light and moisture.

904 **17 PATIENT COUNSELING INFORMATION**

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

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

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

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

920 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

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

930 Suicidal Thoughts and Behaviors

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

941 Severe Allergic Reactions

942 Educate patients on the symptoms of hypersensitivity and to discontinue ZYBAN if they have a
943 severe allergic reaction to ZYBAN.

944 Seizure

945 Instruct patients to discontinue ZYBAN and not restart it if they experience a seizure while on
946 treatment. Advise patients that the excessive use or abrupt discontinuation of alcohol,

947 benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure.
948 Advise patients to minimize or avoid use of alcohol.

949 Angle-Closure Glaucoma

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

957 Bupropion-Containing Products

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

966 Potential for Cognitive and Motor Impairment

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

972 Concomitant Medications

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

976 Pregnancy

977 Advise patients to notify their healthcare provider if they become pregnant or intend to become
978 pregnant during therapy.

979 Precautions for Nursing Mothers

980 Advise patients that ZYBAN is present in human milk in small amounts.

981 Storage Information

982 Instruct patients to store ZYBAN at room temperature, between 59°F and 86°F (15°C to 30°C)
983 and keep the tablets dry and out of the light.

984 Administration Information

985 Instruct patients to swallow ZYBAN tablets whole so that the release rate is not altered. Do not
986 chew, divide, or crush tablets; they are designed to slowly release drug in the body. When
987 patients take more than 150 mg per day, instruct them to take ZYBAN in 2 doses at least 8 hours
988 apart, to minimize the risk of seizures. Instruct patients if they miss a dose, not to take an extra
989 tablet to make up for the missed dose and to take the next tablet at the regular time because of the
990 dose-related risk of seizure. ZYBAN can be taken with or without food. Advise patients that
991 ZYBAN tablets may have an odor.

992

993 ZYBAN, WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL are registered trademarks of
994 the GSK group of companies. The other brands listed are trademarks of their respective owners
995 and are not trademarks of the GSK group of companies. The makers of these brands are not
996 affiliated with and do not endorse the GSK group of companies or its products.

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1001 GlaxoSmithKline

1002 Research Triangle Park, NC 27709

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MEDICATION GUIDE
ZYBAN® (zi ban)
(bupropion hydrochloride)
Sustained-Release Tablets

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

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

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

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

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

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

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

- 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

1046

1047 When you try to quit smoking, with or without ZYBAN, you may have symptoms
 1048 that may be due to nicotine withdrawal, including urge to smoke, depressed mood,
 1049 trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty
 1050 concentrating, restlessness, decreased heart rate, and increased appetite or weight
 1051 gain. Some people have even experienced suicidal thoughts when trying to quit
 1052 smoking without medication. Sometimes quitting smoking can lead to worsening of
 1053 mental health problems that you already have, such as depression.

1054

1055 Before taking ZYBAN, tell your healthcare provider if you have ever had depression
 1056 or other mental illnesses. You should also tell your healthcare provider about any
 1057 symptoms you had during other times you tried to quit smoking, with or without
 1058 ZYBAN.

1059

1060 **Antidepressant Medicines, Depression and Other Serious Mental Illnesses,**
 1061 **and Suicidal Thoughts or Actions**

1062

1063 Although ZYBAN is not a treatment for depression, it contains bupropion, the same
 1064 active ingredient as the antidepressant medications WELLBUTRIN[®], WELLBUTRIN[®]
 1065 SR, and WELLBUTRIN XL[®].

1066

1067 This section of the Medication Guide is only about the risk of suicidal thoughts and
 1068 actions with antidepressant medicines.

1069

1070 **What is the most important information I should know about**
 1071 **antidepressant medicines, depression and other serious mental illnesses,**
 1072 **and suicidal thoughts or actions?**

- 1073 **1. Antidepressant medicines may increase suicidal thoughts or actions in**
 1074 **some children, teenagers, or young adults within the first few months of**
 1075 **treatment.**

1076 **2. Depression or other serious mental illnesses are the most important**
1077 **causes of suicidal thoughts and actions. Some people may have a**
1078 **particularly high risk of having suicidal thoughts or actions.** These include
1079 people who have (or have a family history of) bipolar illness (also called manic-
1080 depressive illness) or suicidal thoughts or actions.

1081 **3. How can I watch for and try to prevent suicidal thoughts and actions in**
1082 **myself or a family member?**

- 1083 • Pay close attention to any changes, especially sudden changes, in mood,
1084 behaviors, thoughts, or feelings. This is very important when an
1085 antidepressant medicine is started or when the dose is changed.
- 1086 • Call your healthcare provider right away to report new or sudden changes in
1087 mood, behavior, thoughts, or feelings.
- 1088 • Keep all follow-up visits with your healthcare provider as scheduled. Call the
1089 healthcare provider between visits as needed, especially if you have concerns
1090 about symptoms.

1091
1092 **Call your healthcare provider right away if you or your family member has**
1093 **any of the following symptoms, especially if they are new, worse, or worry**
1094 **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

1096 **What else do I need to know about antidepressant medicines?**

- 1097 • **Never stop an antidepressant medicine without first talking to a**
1098 **healthcare provider.** Stopping an antidepressant medicine suddenly can cause
1099 other symptoms.
- 1100 • **Antidepressants are medicines used to treat depression and other**
1101 **illnesses.** It is important to discuss all the risks of treating depression and also
1102 the risks of not treating it. Patients and their families or other caregivers should
1103 discuss all treatment choices with the healthcare provider, not just the use of
1104 antidepressants.
- 1105 • **Antidepressant medicines have other side effects.** Talk to the healthcare
1106 provider about the side effects of the medicine prescribed for you or your family
1107 member.

- 1108 • **Antidepressant medicines can interact with other medicines.** Know all of
1109 the medicines that you or your family member takes. Keep a list of all medicines
1110 to show the healthcare provider. Do not start new medicines without first
1111 checking with your healthcare provider.

1112

1113 It is not known if ZYBAN is safe and effective in children under the age of 18.

1114

1115 **What Other Important Information Should I Know About ZYBAN?**

1116

- 1117 • **Seizures: There is a chance of having a seizure (convulsion, fit) with**
1118 **ZYBAN, especially in people:**
- 1119 • with certain medical problems.
 - 1120 • who take certain medicines.

1121

1122 The chance of having seizures increases with higher doses of ZYBAN. For more
1123 information, see the sections “Who should not take ZYBAN?” and “What should I
1124 tell my healthcare provider before taking ZYBAN?” Tell your healthcare provider
1125 about all of your medical conditions and all the medicines you take. **Do not**
1126 **take any other medicines while you are taking ZYBAN unless your**
1127 **healthcare provider has said it is okay to take them.**

1128

1129 **If you have a seizure while taking ZYBAN, stop taking the tablets and**
1130 **call your healthcare provider right away.** Do not take ZYBAN again if you
1131 have a seizure.

1132

- 1133 • **High blood pressure (hypertension). Some people get high blood**
1134 **pressure that can be severe, while taking ZYBAN.** The chance of high blood
1135 pressure may be higher if you also use nicotine replacement therapy (such as a
1136 nicotine patch) to help you stop smoking (see the section of this Medication
1137 Guide called “How should I take ZYBAN?”).

- 1138 • **Manic episodes.** Some people may have periods of mania while taking ZYBAN,
1139 including:

- 1140 • Greatly increased energy
- 1141 • Severe trouble sleeping
- 1142 • Racing thoughts
- 1143 • Reckless behavior
- 1144 • Unusually grand ideas
- 1145 • Excessive happiness or irritability
- 1146 • Talking more or faster than usual

1147 If you have any of the above symptoms of mania, call your healthcare provider.

- 1148 • **Unusual thoughts or behaviors.** Some patients have unusual thoughts or
1149 behaviors while taking ZYBAN, including delusions (believe you are someone
1150 else), hallucinations (seeing or hearing things that are not there), paranoia
1151 (feeling that people are against you), or feeling confused. If this happens to you,
1152 call your healthcare provider.
- 1153 • **Visual problems.**
- 1154 • eye pain
 - 1155 • changes in vision
 - 1156 • swelling or redness in or around the eye
- 1157 Only some people are at risk for these problems. You may want to undergo an
1158 eye examination to see if you are at risk and receive preventative treatment if
1159 you are.
- 1160 • **Severe allergic reactions. Some people can have severe allergic**
1161 **reactions to ZYBAN. Stop taking ZYBAN and call your healthcare**
1162 **provider right away** if you get a rash, itching, hives, fever, swollen lymph
1163 glands, painful sores in the mouth or around the eyes, swelling of the lips or
1164 tongue, chest pain, or have trouble breathing. These could be signs of a serious
1165 allergic reaction.

1166

1167 **What is ZYBAN?**

1168 ZYBAN is a prescription medicine to help people quit smoking.

1169

1170 ZYBAN should be used with a patient support program. It is important to participate
1171 in the behavioral program, counseling, or other support program your healthcare
1172 professional recommends.

1173

1174 Quitting smoking can lower your chances of having lung disease, heart disease, or
1175 getting certain types of cancer that are related to smoking.

1176

1177 **Who should not take ZYBAN?**

1178 **Do not take ZYBAN if you:**

- 1179 • have or had a seizure disorder or epilepsy.
- 1180 • have or had an eating disorder such as anorexia nervosa or bulimia.
- 1181 • **are taking any other medicines that contain bupropion, including**
1182 **WELLBUTRIN, WELLBUTRIN SR, WELLBUTRIN XL, APLENZIN[®], or**
1183 **FORFIVO XL[®].** Bupropion is the same active ingredient that is in ZYBAN.
- 1184 • drink a lot of alcohol and abruptly stop drinking, or take medicines called
1185 sedatives (these make you sleepy), benzodiazepines, or anti-seizure medicines,
1186 and you stop taking them all of a sudden.

- 1187 • take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or
1188 pharmacist if you are not sure if you take an MAOI, including the antibiotic
1189 linezolid.
- 1190 • **do not take an MAOI within 2 weeks of stopping ZYBAN unless**
1191 **directed to do so by your healthcare provider.**
- 1192 • **do not start ZYBAN if you stopped taking an MAOI in the last 2 weeks**
1193 **unless directed to do so by your healthcare provider.**
- 1194 • are allergic to the active ingredient in ZYBAN, bupropion, or to any of the
1195 inactive ingredients. See the end of this Medication Guide for a complete list of
1196 ingredients in ZYBAN.

1197

1198 **What should I tell my healthcare provider before taking ZYBAN?**

1199 Tell your healthcare provider if you have ever had depression, suicidal thoughts or
1200 actions, or other mental health problems. You should also tell your healthcare
1201 provider about any symptoms you had during other times you tried to quit
1202 smoking, with or without ZYBAN. See “Quitting Smoking, Quit-Smoking
1203 Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts
1204 or Actions.”

1205

- 1206 • **Tell your healthcare provider about your other medical conditions,**
1207 **including if you:**
- 1208 • have liver problems, especially cirrhosis of the liver.
 - 1209 • have kidney problems.
 - 1210 • have, or have had, an eating disorder such as anorexia nervosa or bulimia.
 - 1211 • have had a head injury.
 - 1212 • have had a seizure (convulsion, fit).
 - 1213 • have a tumor in your nervous system (brain or spine).
 - 1214 • have had a heart attack, heart problems, or high blood pressure.
 - 1215 • are a diabetic taking insulin or other medicines to control your blood sugar.
 - 1216 • drink alcohol.
 - 1217 • abuse prescription medicines or street drugs.
 - 1218 • are pregnant or plan to become pregnant.
 - 1219 • are breastfeeding. ZYBAN passes into your milk in small amounts
- 1220 • **Tell your healthcare provider about all the medicines you take,** including
1221 prescription, over-the-counter medicines, vitamins, and herbal supplements.
1222 Many medicines increase your chances of having seizures or other serious side
1223 effects if you take them while you are taking ZYBAN.

1224

1225 **How should I take ZYBAN?**

- 1226 • Start ZYBAN before you stop smoking to give ZYBAN time to build up in your
1227 body. It takes about 1 week for ZYBAN to start working.
- 1228 • Pick a date to stop smoking that is during the second week you are taking
1229 ZYBAN.
- 1230 • Take ZYBAN exactly as prescribed by your healthcare provider. Do not change
1231 your dose or stop taking ZYBAN without talking with your healthcare provider
1232 first.
- 1233 • ZYBAN is usually taken for 7 to 12 weeks. Your healthcare provider may decide
1234 to prescribe ZYBAN for longer than 12 weeks to help you stop smoking. Follow
1235 your healthcare provider's instructions.
- 1236 • **Swallow ZYBAN tablets whole. Do not chew, cut, or crush ZYBAN**
1237 **tablets.** If you do, the medicine will be released into your body too quickly. If
1238 this happens you may be more likely to get side effects including seizures. **Tell**
1239 **your healthcare provider if you cannot swallow tablets.**
- 1240 • ZYBAN tablets may have an odor. This is normal.
- 1241 • Take your doses of ZYBAN at least 8 hours apart.
- 1242 • You may take ZYBAN with or without food.
- 1243 • It is not dangerous to smoke and take ZYBAN at the same time. But, you will
1244 lower your chance of breaking your smoking habit if you smoke after the date
1245 you set to stop smoking.
- 1246 • You may use ZYBAN and nicotine patches (a type of nicotine replacement
1247 therapy) at the same time, following the precautions below.
- 1248 • You should only use ZYBAN and nicotine patches together under the care of
1249 your healthcare provider. Using ZYBAN and nicotine patches together may
1250 raise your blood pressure, and sometimes this can be severe.
- 1251 • Tell your healthcare provider if you plan to use nicotine patches. Your
1252 healthcare provider should check your blood pressure regularly if you use
1253 nicotine patches with ZYBAN to help you quit smoking.
- 1254 • If you miss a dose, do not take an extra dose to make up for the dose you
1255 missed. Wait and take your next dose at the regular time. **This is very**
1256 **important.** Too much ZYBAN can increase your chance of having a seizure.
- 1257 • If you take too much ZYBAN, or overdose, call your local emergency room or
1258 poison control center right away.
- 1259 **Do not take any other medicines while taking ZYBAN unless your**
1260 **healthcare provider has told you it is okay.**
- 1261
- 1262 **What should I avoid while taking ZYBAN?**
- 1263 • Limit or avoid using alcohol during treatment with ZYBAN. If you usually drink a
1264 lot of alcohol, talk with your healthcare provider before suddenly stopping. If

1265 you suddenly stop drinking alcohol, you may increase your chance of having
1266 seizures.
1267 • Do not drive a car or use heavy machinery until you know how ZYBAN affects
1268 you. ZYBAN can affect your ability to do these things safely.

1269
1270 **What are possible side effects of ZYBAN?**

1271 ZYBAN can cause serious side effects. See the sections at the beginning of this
1272 Medication Guide for information about serious side effects of ZYBAN.

1273
1274 The most common side effects of ZYBAN include:

- 1275 • trouble sleeping
- 1276 • stuffy nose
- 1277 • dry mouth
- 1278 • dizziness
- 1279 • feeling anxious
- 1280 • nausea
- 1281 • constipation
- 1282 • joint aches

1283 If you have trouble sleeping, do not take ZYBAN too close to bedtime.

1284
1285 Tell your healthcare provider right away about any side effects that bother you.

1286
1287 These are not all the possible side effects of ZYBAN. For more information, ask your
1288 healthcare provider or pharmacist.

1289
1290 Call your doctor for medical advice about side effects. You may report side effects
1291 to FDA at 1-800-FDA-1088.

1292
1293 You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

1294
1295 **How should I store ZYBAN?**

- 1296 • Store ZYBAN at room temperature between 59°F and 86°F (15°C to 30°C).
- 1297 • Keep ZYBAN dry and out of the light.

1298
1299 **Keep ZYBAN and all medicines out of the reach of children.**

1300
1301 **General information about ZYBAN**

1302 Medicines are sometimes prescribed for purposes other than those listed in a
1303 Medication Guide. Do not use ZYBAN for a condition for which it was not prescribed.

1304 Do not give ZYBAN to other people, even if they have the same symptoms you
1305 have. It may harm them.

1306
1307 If you take a urine drug screening test, ZYBAN may make the test result positive
1308 for amphetamines. If you tell the person giving you the drug screening test that
1309 you are taking ZYBAN, they can do a more specific drug screening test that should
1310 not have this problem.

1311
1312 This Medication Guide summarizes important information about ZYBAN. If you
1313 would like more information, talk with your healthcare provider. You can ask your
1314 healthcare provider or pharmacist for information about ZYBAN that is written for
1315 health professionals.

1316
1317 For more information about ZYBAN, call 1-888-825-5249.

1318
1319 **What are the ingredients in ZYBAN?**

1320 Active ingredient: bupropion hydrochloride.

1321
1322 Inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose,
1323 magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80
1324 and titanium dioxide. The tablets are printed with edible black ink. In addition, the
1325 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

1326
1327 This Medication Guide has been approved by the U.S. Food and Drug
1328 Administration.

1329
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1344 June 2016

1345 ZYB:XXMG