PRESCRIBING INFORMATION

ZYBAN®
(bupropion hydrochloride)
Sustained-Release Tablets

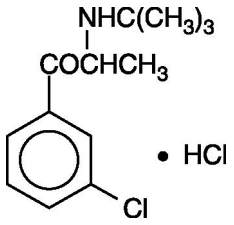
Suicidality in Children and Adolescents

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

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

DESCRIPTION

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



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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

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

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

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

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

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

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

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%.

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

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

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

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

The second study showed that there were no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by 28% for hydroxybupropion and 50% for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 21 hours later for threo/erythrohydrobupropion. The mean half-lives for

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

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

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

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

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

CLINICAL TRIALS

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

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

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

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

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

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

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

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

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

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

Table 2. Comparative Trial: Quit Rates by Treatment Group

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

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

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

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

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

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

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

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

Table 3. COPD Trial: Quit Rates by Treatment Group

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

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

INDICATIONS AND USAGE

ZYBAN is indicated as an aid to smoking cessation treatment.

CONTRAINDICATIONS

ZYBAN is contraindicated in patients with a seizure disorder.

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

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

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

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

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

WARNINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1,000) in depressed patients treated at doses in a range of 300 to 450 mg/day. In addition, the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day.
- **Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.**
- **Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.**
- **Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.**

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

- **the total daily dose of ZYBAN does *not* exceed 300 mg (the maximum recommended dose for smoking cessation), and**
- **the recommended daily dose for most patients (300 mg/day) is administered in divided doses (150 mg twice daily).**
- **No single dose should exceed 150 mg to avoid high peak concentrations of bupropion and/or its metabolites.**

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Information for Patients: 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. Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ZYBAN and should counsel them in its appropriate use. A patient Medication Guide About Using Antidepressants in Children and Teenagers is available for ZYBAN. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Additional important information concerning ZYBAN is provided in a tear-off leaflet entitled “Patient Information" at the end of this labeling.

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

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

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

Laboratory Tests: There are no specific laboratory tests recommended.

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

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

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

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

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

Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., 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), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS (see also WARNINGS and PRECAUTIONS)

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

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

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

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

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

Table 4. Treatment-Emergent Adverse Event Incidence in the Dose-Response Trial*

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

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

Table 5. Treatment-Emergent Adverse Event Incidence in the Comparative Trial*

Adverse Experience (COSTART Term)	ZYBAN 300 mg/day (n = 243) %	Nicotine Transdermal System (NTS) 21 mg/day (n = 243) %	ZYBAN and NTS (n = 244) %	Placebo (n = 159) %
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[†]	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

[*] Selected adverse events with an incidence of at least 1% of patients treated with either ZYBAN, NTS, or the combination of ZYBAN and NTS and more frequent than in the placebo group.
[†] Patients randomized to ZYBAN or placebo received placebo patches.

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

Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion: In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion.

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

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

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

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

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

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

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

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

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

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

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

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

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

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

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

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

DRUG ABUSE AND DEPENDENCE

ZYBAN is likely to have a low abuse potential.

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

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

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

OVERDOSAGE

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

HOW SUPPLIED

ZYBAN Sustained-Release Tablets, 150 mg of bupropion hydrochloride, are purple, round, biconvex, film-coated tablets printed with "ZYBAN 150" in bottles of 60 (NDC 0173-0556-02) tablets and the ZYBAN Advantage Pack® containing 1 bottle of 60 (NDC 0173-0556-01) tablets.

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

Medication Guide

ZYBAN® (zi ban)

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

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

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

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

1. There is a Risk of Suicidal Thoughts or Actions

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

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

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

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

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

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

2. How to Try to Prevent Suicidal Thoughts and Actions

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

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

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

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

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

3. You Should Watch For Certain Signs if Your Child is Taking an Antidepressant

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

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

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

4. There are Benefits and Risks When Using Antidepressants

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

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

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

Of all antidepressants, only fluoxetine (Prozac®)* has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®)*, sertraline (Zoloft®)*, fluvoxamine, and clomipramine (Anafranil®)*.

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

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

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

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

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

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

Patient Information

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

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

What is the most important information I should know about ZYBAN?
There is a chance of having a seizure (convulsion, fit) with ZYBAN, especially in people:

- with certain medical problems.
- who take certain medicines.

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

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

What is important information I should know and share with my family about taking antidepressants?
Although ZYBAN is not a treatment for depression, it contains the same active ingredient as the antidepressant medications WELLBUTRIN®, WELLBUTRIN SR®, and WELLBUTRIN XL®. Therefore, you should be aware of the following information. Patients taking antidepressants, and their families, should watch out for worsening depression or thoughts of suicide. Also watch out for sudden or severe changes in feelings such as feeling anxious, agitated, panicky, irritable,

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

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

What is ZYBAN?

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

Who should not take ZYBAN?

Do not take ZYBAN if you:

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

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

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

What should I tell my doctor before using ZYBAN?

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

- **are pregnant or plan to become pregnant**. It is not known if ZYBAN can harm your unborn baby. If you can use ZYBAN while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
- **are breastfeeding**. ZYBAN passes through your milk. It is not known if ZYBAN can harm your baby.
- **have liver problems,** especially cirrhosis of the liver.
- have kidney problems.
- have an eating disorder such as anorexia nervosa or bulimia.
- have had a head injury.
- have had a seizure (convulsion, fit).
- have a tumor in your nervous system (brain or spine).
- have had a heart attack, heart problems, or high blood pressure.
- are a diabetic taking insulin or other medicines to control your blood sugar.
- drink a lot of alcohol.
- abuse prescription medicines or street drugs.

- **Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines increase your chances of getting seizures or other serious side effects if you take them while you are using ZYBAN.

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

How should I take ZYBAN?

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

How long should I take ZYBAN?

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

When should I stop smoking?

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

Can I smoke while taking ZYBAN?

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

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

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

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

What should I avoid while taking ZYBAN?

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

What are possible side effects of ZYBAN?

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

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

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

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

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

How should I store ZYBAN?

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

General Information about ZYBAN.

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

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

What are the ingredients in ZYBAN?

Active ingredient: bupropion hydrochloride.

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

*The following are registered trademarks of their respective manufacturers: Nardil®/Warner Lambert Company; Marplan®/Oxford Pharmaceutical Services, Inc.

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