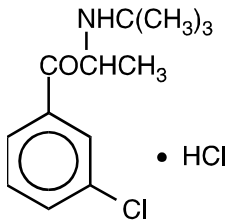
(S-018) ~~PRODUCT~~ PRESCRIBING INFORMATION

ZYBAN®

(bupropion hydrochloride)

Sustained-Release Tablets

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 $C_{13}H_{18}ClNO \cdot HCl$. 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 is 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, hydroxypropyl methylcellulose, 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 two-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 two 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 1950 L (20% CV).

Metabolism: (S-013/AL) Bupropion is extensively metabolized in humans. ~~There are three active metabolites: hydroxybupropion and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via hydroxylation of the *tert*-butyl group of bupropion and/or reduction of the carbonyl group.~~ 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; ~~h~~ However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion ~~comparable in potency to bupropion~~, while ~~the other metabolites~~ threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. ~~are one tenth to one half as potent~~. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion. ~~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.~~

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).

(S-013/AL) 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 ~~The~~ 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.

(S-013/AL) 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 two 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 two 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.

(S-013/AL) ~~Bupropion and its metabolites exhibit linear kinetics following chronic administration of 150 to 300 mg/day.~~

Population Subgroups: Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure, 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 ~~a~~ 2 single-dose stud~~y~~ies, 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 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 (~~28.7~~ 29 hours in patients with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately ~~65~~ 69% lower.

For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately ~~32~~ 31% lower. The mean AUC increased by ~~61~~ 28% for hydroxybupropion and ~~163~~ 50% for threo/erythrohydrobupropion.

The median T_{max} was observed 19 hours later for hydroxybupropion and ~~31~~ 21 hours later for threo/erythrohydrobupropion. The mean half-lives ~~were~~ for hydroxybupropion and threo/erythrohydrobupropion were increased 2- and ~~5~~ 4-fold respectively in patients with severe hepatic cirrhosis compared to healthy volunteers (see WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal: The effect of renal disease on the pharmacokinetics of bupropion has not been studied. The elimination of the major metabolites of bupropion may be affected by reduced renal function.

Left Ventricular Dysfunction: During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of congestive heart failure [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 three 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 three placebo-controlled, double-blind trials in nondepressed chronic cigarette smokers (n = 1940, ≥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 three clinical centers. Patients in this study were treated for 7 weeks with one of three 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 four 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 three 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 five 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.

S-012 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 $FEV_1 \geq 35\%$, $FEV_1/FVC < 70\%$ 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

4-Week Abstinence Period	Treatment Groups	
	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, WELLBUTRIN SR, 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.

(**S-018/CBE)** ZYBAN is containdicated 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: Patients should be made aware that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression, and that ZYBAN should not be used in combination with WELLBUTRIN, WELLBUTRIN SR, or any other medications that contain bupropion.

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 concurrent medications, which must be considered in selection of patients for therapy with ZYBAN. (S-016/CBE) Zyban should be discontinued and not started 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% (1/1000). This incidence was prospectively determined during an 8-week treatment exposure in approximately 3100 depressed patients. Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (4/1000) 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, (S-013/CBE) 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 (S-018/CBE) or sedatives (including benzodiazepines) ; ~~abrupt withdrawal from alcohol or other sedatives~~; 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) (S-018/CBE) ~~and treatment regimens (e.g., abrupt discontinuation of benzodiazepines)~~ 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.) (S-018/CBE) ~~or treatment regimens (e.g., abrupt discontinuation of a benzodiazepine)~~ that lower seizure threshold.

(S-013/CBE/AL)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 three 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.

***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 one 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 two patients for exacerbation of baseline hypertension.

(S-013/CBE/AL) ***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).

(S-013/CBE/AL) ***Renal or Hepatic Impairment:*** ~~Because bupropion hydrochloride and its metabolites are almost completely excreted through the kidney and metabolites are likely to undergo conjugation in the liver prior to urinary excretion, treatment of patients with renal or hepatic impairment should be initiated at reduced dosage~~ No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and 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 bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible ~~toxic~~ adverse effects that could indicate high drug or metabolite levels ~~of elevated blood and tissue levels of drug and metabolites~~.

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the **(S-018)**~~separate~~ tear-off leaflet provided for patients. Physicians are advised to review the leaflet with their patients and to emphasize that ZYBAN contains the same active ingredient found in WELLBUTRIN and WELLBUTRIN SR used to treat depression and that ZYBAN should not be used in conjunction with WELLBUTRIN, WELLBUTRIN SR, 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 cytochrome P450IIB6 (CYP2B6) isoenzyme. Therefore, the potential exists for a drug interaction between ZYBAN and drugs that affect the CYP2B6 isoenzyme (e.g., orphenadrine and cyclophosphamide). 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.

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 theohydro- 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 two-, five- and two-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).

(S-018/CBE) ***Levodopa and Amantadine:*** Limited clinical data suggest a higher incidence of adverse experiences in patients receiving ~~concurrent administration of~~ bupropion ~~and~~ 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.

(S-018/CBE) ***Drugs that Lower Seizure Threshold:*** Concurrent administration of ZYBAN and agents (e.g., antipsychotics, antidepressants, theophylline, systemic steroids, etc.) ~~or treatment regimens (e.g., abrupt discontinuation of benzodiazepines)~~ that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS).

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

(S-014, S-014/AF) ***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.

(S-018/CBE) ***Alcohol***: In post marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerence 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 ten and two 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 three to ten 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 (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three 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 B:*** Teratology studies have been performed at doses up to 450 mg/kg in rats (approximately 14 times the MRHD on a mg/m^2 basis), and at doses up to 150 mg/kg in rabbits (approximately 10 times the MRHD on a mg/m^2 basis). There is no evidence of impaired fertility or harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. 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, **(S-016/CBE)** ~~Glaxo Wellcome Inc~~. 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: Clinical trials with ZYBAN did not include individuals under the age of 18. Therefore, the safety and efficacy in a pediatric smoking population have not been established. The immediate-release formulation of bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tolerated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients.

Geriatric Use: Of the approximately 6000 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).

(S-013/CBE) 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 ~~Use in Patients with Systemic Illness~~ 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 five 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 3 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 4 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 3: 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 4: 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	9	3	9	4
concentration	10	2	8	6
Dizziness	4	<1	2	2
Nervousness	1	<1	2	0
Tremor	<1	1	2	1
Dysphoria				
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	11	17	15	7
reaction†	4	3	3	2
Rash	3	1	5	1
Pruritus	2	0	2	0
Urticaria				
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.

In the long-term maintenance trial, which evaluated chronic administration of ZYBAN for up to 1 year, ZYBAN was well tolerated. Adverse events 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 = 1013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion sustained-release tablets (n = 3100). All treatment-emergent adverse events are included except those listed in Tables 3 and 4, 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 two 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 1/1000 patients, while rare events are those occurring in less than 1/1000 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.

(S-014, S-014/AF) ***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), akinesia, aphasia, coma, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, **(S-018/CBE**) hallucinations hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, 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: There has been very limited experience with overdosage of the sustained-release formulation of bupropion; three such cases were reported during clinical trials in depressed patients. One patient ingested 3000 mg of bupropion sustained-release tablets and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a “handful” of bupropion sustained-release tablets and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3600 mg of bupropion sustained-release tablets and a bottle

of wine; the patient experienced nausea, visual hallucinations, and “grogginess.” None of the patients experienced further sequelae.

There has been extensive experience with overdosages of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials in depressed patients. Twelve patients ingested 850 to 4200 mg and recovered without significant sequelae. Another patient who ingested 9000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae.

Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive 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:

ZYBAN: ***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). **(S-016/CBE)** 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.

(S-013/CBE) Dosage Adjustment for Patients with Impaired Hepatic Function (i): 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).

(S-013/CBE) Dosage Adjustment for Patients with Impaired Renal Function (ii): 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.

PATIENT INFORMATION: The following wording is contained in a **(S-018/CBE)** ~~separate~~ tear-off leaflet provided for patients.

Information for the Patient

ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets

Please read this information before you start taking ZYBAN. Also read this leaflet each time you renew your prescription, in case anything has changed. This information is not intended to take the place of discussions between you and your doctor. You and your doctor should discuss ZYBAN as part of your plan to stop smoking. Your doctor has prescribed ZYBAN for your use only. Do not let anyone else use your ZYBAN.

IMPORTANT WARNING:

There is a chance that approximately 1 out of every 1000 people taking bupropion hydrochloride, the active ingredient in ZYBAN, will have a seizure. The chance of this happening increases if you:

- have or have had a seizure disorder (for example, epilepsy);
- have or have had an eating disorder (for example, bulimia or anorexia nervosa);
- **(S-018/CBE)** are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines):
- take more than the recommended amount of ZYBAN; or
- take other medicines with the same active ingredient that is in ZYBAN, such as WELLBUTRIN® (bupropion hydrochloride) Tablets and WELLBUTRIN SR® (bupropion hydrochloride) Sustained-Release Tablets. (Both of these medicines are used to treat depression.)

You can reduce the chance of experiencing a seizure by following your doctor's directions on how to take ZYBAN. **(S-016/CBE)** If you experience a seizure while taking ZYBAN, stop taking the tablets immediately, contact your doctor, and do not restart ZYBAN.

In addition, tell your doctor if you have or have had other medical conditions. You should also discuss with your doctor whether ZYBAN is right for you.

1. 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.

2. Who should not take ZYBAN?

You should not take ZYBAN if you:

- **(S-016/CBE)** have or have had a seizure disorder (for example, epilepsy).
- are already taking WELLBUTRIN, WELLBUTRIN SR, or any other medicines that contain bupropion hydrochloride.
- have or have had an eating disorder (for example, bulimia or anorexia nervosa).
- **(S-018/CBE)** are abruptly discontinuing use of alcohol or sedatives (including benzodiazepines):
- are currently taking or have recently taken a monoamine oxidase inhibitor (MAOI).
- are allergic to bupropion.

3. Are there special concerns for women?

ZYBAN is not recommended for women who are pregnant or **(S-018/CBE)** ~~breast-feeding~~ breastfeeding Women should notify their doctor if they become pregnant or intend to become pregnant while taking ZYBAN.

4. (S-013/CBE) Are there any concerns for patients with liver or kidney disease? (iii)

If you have liver or kidney disease, tell your doctor before taking ZYBAN. Depending on the severity of your condition, your doctor may need to adjust your dosage.

(S-016) Are there any concerns for patients with liver or kidney ~~disease~~ problems? . If you have liver or kidney ~~disease~~ problems , tell your doctor before taking ZYBAN. Depending on the severity of your condition, your doctor may need to adjust your dosage.

5. How should I take ZYBAN?

- You should take ZYBAN as directed by your doctor. The usual recommended dosing is to take one 150-mg tablet in the morning for the first 3 days. On the fourth day, begin taking one 150-mg tablet in the morning and one 150-mg tablet in the early evening. Doses should be taken at least 8 hours apart.

- **Never take an "extra" dose of ZYBAN.** If you forget to take a dose, do not take an extra tablet to "catch up" for the dose you forgot. Wait and take your next tablet at the regular time. Do not take more tablets than your doctor prescribed. This is important so you do not increase your chance of having a seizure.
- It is important to swallow ZYBAN Tablets whole. Do not chew, divide, or crush tablets.

6. 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.

7. 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.

8. 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.

9. 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 **(S-016/CBE)** sometimes severely. Tell your doctor if you are planning to use nicotine replacement therapy because y~~Y~~our 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.

10. What are possible side effects of ZYBAN?

Like all medicines, ZYBAN may cause side effects. **(S-016/CBE)** Do not rely on this summary alone for information about side effects. Your doctor can discuss with you a more complete list of side effects that may be relevant to you.

- Hypertension (high blood pressure), in some cases severe, has been reported in patients taking ZYBAN alone and in combination with nicotine replacement therapy (for example, a nicotine patch, see Question #10).

- The most common side effects include dry mouth and difficulty sleeping. These side effects are generally mild and often disappear after a few weeks. If you have difficulty sleeping, avoid taking your medicine too close to bedtime.
- The most common side effects that caused people to stop taking ZYBAN during clinical studies were shakiness and skin rash.
- Stop taking ZYBAN and contact your doctor or health care professional if you have signs of an allergic reaction such as a rash, hives, or difficulty in breathing. **(S-016/CBE)** It is not possible to predict whether a mild rash will develop into a more serious reaction. Therefore, if you experience a skin rash, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, or swelling of lips or tongue, tell a doctor immediately, since these symptoms may be the first signs of a serious reaction. Discuss any other troublesome side effects with your doctor.
- Use caution before driving a car or operating complex, hazardous machinery until you know if ZYBAN affects your ability to perform these tasks.

11. Can I drink alcohol while I am taking ZYBAN?

It is best to not drink alcohol at all or to drink very little while taking ZYBAN. If you drink a lot of alcohol and suddenly stop, you may increase your chance of having a seizure. **(S-018/CBE)** Some people have reported lower alcohol tolerance during treatment with ZYBAN. Therefore, it is important to discuss your use of alcohol with your doctor before you begin taking ZYBAN.

12. Will ZYBAN affect other medicines I am taking?

ZYBAN may affect other medicines you're taking. It is important not to take medicines that may increase the chance for you to have a seizure. Therefore, you should make sure that your doctor knows about all medicines—prescription or over-the-counter—you are taking or plan to take.

13. Do ZYBAN Tablets have a characteristic odor?

ZYBAN Tablets may have a characteristic odor. If present, this odor is normal.

14. How should I store ZYBAN?

- Store ZYBAN at room temperature, out of direct sunlight.

- Keep ZYBAN in a tightly closed container.
- Keep ZYBAN out of the reach of children.

This summary provides important information about ZYBAN. This summary cannot replace the more detailed information that you need from your doctor. If you have any questions or concerns about either ZYBAN or smoking cessation, talk to your doctor or other health care professional.

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