CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-515

APPROVED LABELING

PRESCRIBING INFORMATION

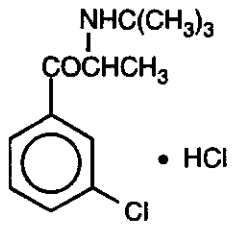
WELLBUTRIN XL™

(bupropion hydrochloride extended-release tablets)

"Patient Information" enclosed.

DESCRIPTION

WELLBUTRIN XL (bupropion hydrochloride), an antidepressant of the aminoketone class, is 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 designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is $C_{13}H_{18}ClNO{\bullet}HCl$. 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:



WELLBUTRIN XL Tablets are supplied for oral administration as 150-mg and 300-mg, creamy-white to pale yellow extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: ethylcellulose aqueous dispersion (NF), glyceryl behenate, methacrylic acid copolymer dispersion (NF), polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black ink.

The insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, 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. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (±9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days.

In a study comparing 14-day dosing with WELLBUTRIN XL Tablets 300 mg once daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion).

Absorption: Following oral administration of WELLBUTRIN XL Tablets to healthy volunteers, time to peak plasma concentrations for bupropion was approximately 5 hours and food did not affect the C_{max} or AUC of bupropion.

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.

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).

In humans, peak plasma concentrations of hydroxybupropion occur approximately 7 hours after administration of WELLBUTRIN XL. Following administration of WELLBUTRIN XL, peak plasma concentrations of hydroxybupropion are approximately 7 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 13 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, approximately 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.4 and 7 times that of bupropion, respectively.

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

Elimination: 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. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

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 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 about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-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 CHF or an enlarged heart on

x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

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 daily 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.

Smokers: 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 bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

CLINICAL TRIALS

The efficacy of bupropion as a treatment for major depressive disorder was established with the immediate-release formulation of bupropion in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week, placebo-controlled trial in adult outpatients. In the first study, patients were titrated in a bupropion dose range of 300 to 600 mg/day of the immediate-release formulation on a 3 times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included 2 fixed doses of the immediate-release formulation of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of bupropion, but only at the 450-mg/day dose of the immediate-release formulation; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion. This study demonstrated the effectiveness of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

Although there are no independent trials demonstrating the antidepressant effectiveness of WELLBUTRIN XL, studies have demonstrated similar bioavailability of the immediate-release and the extended-release formulations of bupropion under steady-state conditions, i.e., WELLBUTRIN XL 300 mg once daily was shown to have bioavailability that was similar to that

of 100 mg 3 times daily of the immediate-release formulation of bupropion, with regard to both rate and extent of absorption, for parent drug and metabolites.

In a longer-term study, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on bupropion (150 mg twice daily of the sustained-release formulation) were randomized to continuation of their same dose of bupropion or placebo, for up to 44 weeks of observation for relapse. Response during the open phase was defined as CGI Improvement score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients receiving continued bupropion treatment experienced significantly lower relapse rates over the subsequent 44 weeks compared to those receiving placebo.

INDICATIONS AND USAGE

WELLBUTRIN XL is indicated for the treatment of major depressive disorder.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled trials of inpatients and in one 6-week controlled trial of outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) (see CLINICAL PHARMACOLOGY).

A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation.

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use WELLBUTRIN XL for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

WELLBUTRIN XL is contraindicated in patients with a seizure disorder.

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

WELLBUTRIN XL 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.

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

The concurrent administration of WELLBUTRIN XL Tablets 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 WELLBUTRIN XL Tablets.

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

WARNINGS

Patients should be made aware that WELLBUTRIN XL contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN XL should not be used in combination with ZYBAN, or any other medications that contain bupropion, such as WELLBUTRIN SR (bupropion hydrochloride), the sustained-release formulation or WELLBUTRIN (bupropion hydrochloride), the immediate-release formulation.

Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with WELLBUTRIN XL. WELLBUTRIN XL should be discontinued and not restarted in patients who experience a seizure while on treatment.

As both WELLBUTRIN XL and the sustained-release formulation of bupropion (WELLBUTRIN SR) are bioequivalent to the immediate-release formulation of bupropion, the seizure incidence with WELLBUTRIN XL, while not formally evaluated in clinical trials, may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion.

- **Dose: At doses up to 300 mg/day of the sustained-release formulation of bupropion (WELLBUTRIN SR), the incidence of seizure is approximately 0.1% (1/1,000).**

  Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants.

  Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of WELLBUTRIN XL Tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.
- **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 WELLBUTRIN XL Tablets does *not* exceed 450 mg,**
- **the rate of incrementation of dose is gradual.**

WELLBUTRIN XL *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, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

Hepatic Impairment: WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, 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: ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials with WELLBUTRIN SR, the sustained-release formulation of bupropion, experienced agitation, anxiety, and insomnia as shown in Table 1.

Table 1. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs.

Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo.

Psychosis, Confusion, and Other Neuropsychiatric Phenomena: Depressed patients treated with bupropion 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 patients. WELLBUTRIN XL is expected to pose similar risks.

Altered Appetite and Weight: In placebo-controlled studies using WELLBUTRIN SR, the sustained-release formulation of bupropion, patients experienced weight gain or weight loss as shown in Table 2.

Table 2. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials

Weight Change	WELLBUTRIN SR 300 mg/day (n = 339)	WELLBUTRIN SR 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN XL Tablets should be considered.

Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for WELLBUTRIN XL Tablets should be written for the smallest number of tablets consistent with good patient management.

Allergic Reactions: Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. 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 WELLBUTRIN XL 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.

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 pre-existing hypertension.

Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), 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 sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of pre-existing 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 WELLBUTRIN XL Tablets 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: WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose 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: 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 subsequently excreted by the kidneys. WELLBUTRIN XL should be used with caution in patients with renal impairment and a reduced frequency and/or dose 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 adverse effects that could indicate high drug or metabolite levels.

Information for Patients: See the tear-off leaflet at the end of this labeling for Patient Information.

Patients should be made aware that WELLBUTRIN XL contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN XL should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as WELLBUTRIN SR, the sustained-release formulation, and WELLBUTRIN, the immediate-release formulation).

Physicians are advised to discuss the following issues with patients:

Patients should be told that WELLBUTRIN XL should be discontinued and not restarted if they experience a seizure while on treatment.

Patients should be told that any CNS-active drug like WELLBUTRIN XL Tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that WELLBUTRIN XL Tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.

Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with WELLBUTRIN XL. Patients should be advised that the consumption of alcohol should be minimized or avoided.

Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because WELLBUTRIN XL Tablets and other drugs may affect each other's metabolism.

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to swallow WELLBUTRIN XL Tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets.

Patients should be advised that they may notice in their stool something that looks like a tablet. This is normal. The medication in WELLBUTRIN XL is contained in a non-absorbable shell that has been specially designed to slowly release drug in the body. When this process is completed, the empty shell is eliminated from the body.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions: Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs.

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN XL 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. 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 tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin).

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs.

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 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 WELLBUTRIN XL Tablets 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 WELLBUTRIN XL Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed.

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

Alcohol: In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with WELLBUTRIN XL 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/day, respectively. These doses are approximately 7 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/day (approximately 2 to 7 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 cytogenetic studies.

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

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B. Teratology studies have been performed with bupropion immediate-release formulation at dosages up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of 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.

To monitor fetal outcomes of pregnant women exposed to WELLBUTRIN XL, 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 WELLBUTRIN XL Tablets on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN XL Tablets, 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: The safety and effectiveness of WELLBUTRIN XL Tablets in pediatric patients below 18 years old 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 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. 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. 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.)

WELLBUTRIN XL has been demonstrated to have similar bioavailability to the immediate-release formulation of bupropion (see CLINICAL PHARMACOLOGY). The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with WELLBUTRIN SR Tablets, the sustained-release formulation of bupropion. WELLBUTRIN XL has not been

studied in placebo-controlled trials, although it has been studied in non-placebo-controlled clinical bioavailability studies. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation 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).

Incidence in Controlled Trials With Bupropion: ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed in Table 3.

Table 3. Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials

Adverse Event Term	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion, include vomiting, seizures, and sleep disturbances.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion: Table 4 enumerates treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be

compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is provided in the WARNINGS and PRECAUTIONS sections.

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29 **Table 4. Treatment-Emergent Adverse Events in Placebo-Controlled Trials***

Body System/ Adverse Event	WELLBUTRIN SR 300 mg/day (n = 376)	WELLBUTRIN SR 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%
Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	—
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	—
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	—
Nervous system			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%

Irritability	3%	2%	2%
Memory decreased	—	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	—
Amblyopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	—	2%	0%
Vaginal hemorrhage†	0%	2%	—
Urinary tract infection	1%	0%	—

* Adverse events that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse events occurring in greater than 0 but less than 0.5% of patients.

Additional events to those listed in Table 4 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%),

decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials: Adverse events from Table 4 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

300 mg/day of the Sustained-Release Formulation: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of the Sustained-Release Formulation: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

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 the sustained-release formulation of bupropion. 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 the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 1 through 4, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific 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 of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling.

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 WELLBUTRIN XL is unknown.

Body (General): Infrequent were chills, facial edema, musculoskeletal chest 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 postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

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 coadministered with warfarin.

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

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

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

Respiratory: Rare was bronchospasm. Also observed was pneumonia.

Skin: Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism.

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

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Bupropion is not a controlled substance.

Humans: Controlled clinical studies of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability.

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

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-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE

Human Overdose Experience: There has been very limited experience with overdosage of the sustained-release formulation of bupropion (WELLBUTRIN SR Tablets); 3 cases were reported during clinical trials. One patient ingested 3,000 mg of the sustained-release formulation of bupropion and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of WELLBUTRIN SR Tablets (the sustained-release formulation) and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of the sustained-release formulation of bupropion 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 overdosage of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 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 WELLBUTRIN XL, 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

General Dosing Considerations: It is particularly important to administer WELLBUTRIN XL Tablets in a manner most likely to minimize the risk of seizure (see WARNINGS). Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. WELLBUTRIN XL should be swallowed whole and not crushed, divided, or chewed. WELLBUTRIN XL may be taken without regard to meals.

Initial Treatment: The usual adult target dose for WELLBUTRIN XL Tablets is 300 mg/day, given once daily in the morning. Dosing with WELLBUTRIN XL Tablets should begin at 150 mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately

698 tolerated, an increase to the 300-mg/day target dose, given as once daily, may be made as early
699 as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.
700 **Increasing the Dosage Above 300 mg/day:** As with other antidepressants, the full
701 antidepressant effect of WELLBUTRIN XL Tablets may not be evident until 4 weeks of
702 treatment or longer. An increase in dosage to the maximum of 450 mg/day, given as a single
703 dose, may be considered for patients in whom no clinical improvement is noted after several
704 weeks of treatment at 300 mg/day.
705 **Switching Patients from WELLBUTRIN Tablets or from WELLBUTRIN SR**
706 **Sustained-Release Tablets:** When switching patients from WELLBUTRIN Tablets to
707 WELLBUTRIN XL or from WELLBUTRIN SR Sustained-Release Tablets to
708 WELLBUTRIN XL, give the same total daily dose when possible. Patients who are currently
709 being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day)
710 may be switched to WELLBUTRIN XL 300 mg once daily. Patients who are currently being
711 treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg
712 twice daily) may be switched to WELLBUTRIN XL 300 mg once daily.
713 **Maintenance Treatment:** It is generally agreed that acute episodes of depression require
714 several months or longer of sustained pharmacological therapy beyond response to the acute
715 episode. It is unknown whether or not the dose of WELLBUTRIN XL needed for maintenance
716 treatment is identical to the dose needed to achieve an initial response. Patients should be
717 periodically reassessed to determine the need for maintenance treatment and the appropriate dose
718 for such treatment.
719 **Dosage Adjustment for Patients With Impaired Hepatic Function:**
720 WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic
721 cirrhosis. The dose should not exceed 150 mg every other day in these patients.
722 WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including
723 mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in
724 patients with mild to moderate hepatic cirrhosis (see CLINICAL PHARMACOLOGY,
725 WARNINGS, and PRECAUTIONS).
726 **Dosage Adjustment for Patients With Impaired Renal Function:** WELLBUTRIN XL
727 should be used with caution in patients with renal impairment and a reduced frequency and/or
728 dose should be considered (see CLINICAL PHARMACOLOGY and PRECAUTIONS).

729 **HOW SUPPLIED**

730 WELLBUTRIN XL Extended-Release Tablets, 150 mg of bupropion hydrochloride, are
731 creamy-white to pale yellow, round, tablets printed with "WELLBUTRIN XL 150" in bottles of
732 30 tablets (NDC 0173-0730-01).
733 WELLBUTRIN XL Extended-Release Tablets, 300 mg of bupropion hydrochloride, are
734 creamy-white to pale yellow, round, tablets printed with "WELLBUTRIN XL 300" in bottles of
735 30 tablets (NDC 0173-0731-01).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Manufactured by:
Biovail Corporation
Mississauga, ON L5N 8M5, Canada for
GlaxoSmithKline
Research Triangle Park, NC 27709

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September 2003 RL-2017

PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

Patient Information

WELLBUTRIN XL™ (WELL byu trin XL)
(bupropion hydrochloride extended-release tablets)

Read the Patient Information that comes with WELLBUTRIN XL before you start taking WELLBUTRIN XL 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.

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

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

The chance of having seizures increases with higher doses of WELLBUTRIN XL. For more information, see the sections "Who should not take WELLBUTRIN XL?" and "What should I tell my doctor before using WELLBUTRIN XL?" 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 WELLBUTRIN XL unless your doctor has said it is okay to take them.**

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

What is WELLBUTRIN XL?

WELLBUTRIN XL is a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

Who should not take WELLBUTRIN XL?

Do not take WELLBUTRIN XL if you

- have or had a seizure disorder or epilepsy.
- **are taking ZYBAN (used to help people stop smoking) or any other medicines that contain bupropion hydrochloride, such as WELLBUTRIN Tablets or WELLBUTRIN SR Sustained-Release Tablets.** Bupropion is the same active ingredient that is in WELLBUTRIN XL.
- 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 WELLBUTRIN XL, bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in WELLBUTRIN XL.

What should I tell my doctor before using WELLBUTRIN XL?

- **Tell your doctor about your medical conditions.** Tell your doctor if you
  - **are pregnant or plan to become pregnant.** It is not known if WELLBUTRIN XL can harm your unborn baby. If you can use WELLBUTRIN XL while you are pregnant, talk to your doctor about how you can be on the Bupropion Pregnancy Registry.
  - **are breastfeeding.** WELLBUTRIN XL passes through your milk. It is not known if WELLBUTRIN XL 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 having seizures or other serious side effects if you take them while you are using WELLBUTRIN XL.

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

How should I take WELLBUTRIN XL?

- Take WELLBUTRIN XL exactly as prescribed by your doctor.
- **Do not chew, cut, or crush WELLBUTRIN XL tablets.** You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take WELLBUTRIN XL at the same time each day.
- Take your doses of WELLBUTRIN XL at least 24 hours apart.
- You may take WELLBUTRIN XL with or without food.
- 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 WELLBUTRIN XL can increase your chance of having a seizure.
- If you take too much WELLBUTRIN XL, or overdose, call your local emergency room or poison control center right away.
- The WELLBUTRIN XL tablet is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.
- **Do not take any other medicines while using WELLBUTRIN XL unless your doctor has told you it is okay.**
- It may take several weeks for you to feel that WELLBUTRIN XL is working. Once you feel better, it is important to keep taking WELLBUTRIN XL exactly as directed by your doctor. Call your doctor if you do not feel WELLBUTRIN XL is working for you.
- Do not change your dose or stop taking WELLBUTRIN XL without talking with your doctor first.

What should I avoid while taking WELLBUTRIN XL?

- Do not drink a lot of alcohol while taking WELLBUTRIN XL. 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 WELLBUTRIN XL affects you. WELLBUTRIN XL can impair your ability to perform these tasks.

What are possible side effects of WELLBUTRIN XL?

- **Seizures.** Some patients get seizures while taking WELLBUTRIN XL. **If you have a seizure while taking WELLBUTRIN XL, stop taking the tablets and call your doctor right away.** Do not take WELLBUTRIN XL again if you have a seizure.
- **Hypertension (high blood pressure).** Some patients get high blood pressure, sometimes severe, while taking WELLBUTRIN XL. 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.
- **Severe allergic reactions. Stop WELLBUTRIN XL 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 WELLBUTRIN XL, 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 WELLBUTRIN XL are weight loss, loss of appetite, dry mouth, skin rash, sweating, ringing in the ears, shakiness, stomach pain, agitation, anxiety, dizziness, trouble sleeping, muscle pain, nausea, fast heartbeat, sore throat, and urinating more often.

If you have nausea, take your medicine with food. If you have trouble 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 WELLBUTRIN XL. For a complete list, ask your doctor or pharmacist.

How should I store WELLBUTRIN XL?

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

General Information about WELLBUTRIN XL.

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

This leaflet summarizes important information about WELLBUTRIN XL. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about WELLBUTRIN XL that is written for health professionals or you can visit www.wellbutrin-xl.com or call toll-free 888-825-5249.

What are the ingredients in WELLBUTRIN XL?

Active ingredient: bupropion hydrochloride.

Inactive ingredients: ethylcellulose aqueous dispersion (NF), glyceryl behenate, methacrylic acid copolymer dispersion (NF), polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide, and triethyl citrate. The tablets are printed with edible black ink.

Rx only

GlaxoSmithKline

Manufactured by:
Biovail Corporation
Mississauga, ON L5N 8M5, Canada for
GlaxoSmithKline
Research Triangle Park, NC 27709

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September 2003 RL-2017

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Russell Katz
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Supervisory Signer(s)

1. Russell Katz
   28-Aug-2003

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