Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the re-uptake of serotonin. 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 chronic dosing with bupropion hydrochloride extended-release tablets (SR) 150 mg twice daily to the immediate-release formulation of bupropion at 100 mg 3 times daily, peak plasma concentrations of bupropion at steady state for bupropion hydrochloride extended-release tablets (SR) were approximately 85% of those achieved with the immediate-release formulation. There was equivalence for bupropion AUCs, as well as equivalence for both peak plasma concentration and AUCs for all 3 of the detectable bupropion metabolites. Thus, at steady state, bupropion hydrochloride extended-release tablets (SR), given twice daily and the immediate-release formulation of bupropion, given 3 times daily, are essentially bioequivalent for both bupropion and the 3 quantitatively important metabolites.

Absorption

Following oral administration of bupropion hydrochloride extended-release tablets (SR) to healthy volunteers, peak plasma concentrations of bupropion are achieved within 3 hours. Food increased C_max and AUC of bupropion by 11% and 17%, respectively, indicating that there is no clinically significant food effect.

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 or which inhibit/induce the cytochrome P450IIB6 (CYP2B6) isoenzyme such as ritonavir. In a healthy volunteer study, ritonavir at a dose of 100 mg twice daily reduced the AUC and $C_{\text{max}}$ of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%. In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the AUC and the $C_{\text{max}}$ of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer study, KALETRA® (lopinavir 400 mg/ritonavir 100 mg twice daily) decreased bupropion AUC and $C_{\text{max}}$ by 57%. The AUC and $C_{\text{max}}$ of hydroxybupropion were decreased by 50% and 31%, respectively (see PRECAUTIONS, Drug Interactions).

Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is co-administered with drugs metabolized by this isoenzyme (see PRECAUTIONS, Drug Interactions).

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

Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 mg/day 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_{1/2}) 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 threo-hydrobupropion and erythro-hydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythro-hydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythro-hydrobupropion. The mean half-lives for hydroxybupropion and threo/erythro-hydrobupropion 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

There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threo-hydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. A second study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that exposure to a single 150-mg dose of sustained-release bupropion was approximately 2-fold higher in patients with impaired renal function while levels of the hydroxybupropion and threo/erythro-hydrobupropion (combined) metabolites were similar in the 2 groups. The elimination of bupropion and/or the major metabolites of bupropion may be reduced by impaired renal function (see PRECAUTIONS, Renal Impairment).

Left Ventricular Dysfunction
During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites 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 mg/day 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.

INDICATIONS AND USAGE

Bupropion hydrochloride extended-release tablets USP (SR) are 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 depressed inpatients and in one 6-week controlled trial of depressed 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 hydrochloride extended-release tablets USP (SR) in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY). Nevertheless, the physician who elects to use bupropion hydrochloride extended-release tablets USP (SR) for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients with a seizure disorder.

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

Bupropion hydrochloride extended-release tablets (SR) are 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.

Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines).

The concurrent administration of bupropion hydrochloride extended-release tablets (SR) 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 bupropion hydrochloride extended-release tablets (SR).

Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up bupropion hydrochloride extended-release tablets (SR).

WARNINGSClinical Worsening and Suicide Risk in Treating Psychiatric Disorders

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD) or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications

ADVERSE REACTIONS

(See also WARNINGS and PRECAUTIONS.)

The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS is based primarily on data from controlled clinical trials with Bupropion Hydrochloride Extended-Release Tablets (SR). Information on additional adverse events associated with the extended-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see ADVERSE REACTIONS, Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion).
Incidence in Controlled Trials with Bupropion Hydrochloride Extended-Release Tablets (SR)

Adverse Events Associated with Discontinuation of Treatment Among Patients Treated with Bupropion Hydrochloride Extended-Release Tablets (SR)

In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 mg/day and 400 mg/day, respectively, of bupropion hydrochloride extended-release tablets (SR) 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 bupropion hydrochloride extended-release tablets (SR) and at a rate at least twice the placebo rate are listed in Table 4.

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with Bupropion Hydrochloride Extended-Release Tablets (SR)

Table 5 enumerates treatment-emergent adverse events that occurred among patients treated with 300 mg/day and 400 mg/day of bupropion hydrochloride extended-release tablets (SR) and with placebo in placebo-controlled trials. Events that occurred in either the 300-mg/day 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 hydrochloride extended-release tablets (SR) is provided in the WARNINGS and PRECAUTIONS sections.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

Adverse events from Table 5 occurring in at least 5% of patients treated with bupropion hydrochloride extended-release tablets (SR) and at a rate at least twice the placebo rate are listed below for the 300-mg/day and 400-mg/day dose groups.

**Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day:** Anorexia, dry mouth, rash, sweating, tinnitus and tremor.

**Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day:** 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 extended-release (SR) 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 extended-release formulation of bupropion (SR). The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013) or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with bupropion hydrochloride extended-release tablets (SR) (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 2 through 5, 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 extended-release bupropion (SR) are included. The extent to which these events may be associated with bupropion hydrochloride extended-release tablets (SR) are 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 co-administered 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, hypertonía, hyposthesia, suicidal ideation and vertigo. Rare were amnesia, ataxia, derealization and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aggression, aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt 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, increased intraocular pressure 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.

**OVERDOSAGE**

**Human Overdose Experience**

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

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

**Overdosage Management**

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended.

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 bupropion hydrochloride extended-release tablets (SR), 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 bupropion hydrochloride extended-release tablets (SR) 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. Bupropion hydrochloride extended-release tablets (SR) should be swallowed whole and not crushed, divided or chewed, as this may lead to an increased risk of adverse effects including seizures.

**Initial Treatment:** The usual adult target dose for bupropion hydrochloride extended-release tablets (SR) is 300 mg/day, given as 150 mg twice daily. Dosing with bupropion hydrochloride extended-release...
tablets (SR) should begin at 150-mg/day given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, an increase to the 300-mg/day target dose, given as 150 mg twice daily, may be made as early as day 4 of dosing. There should be an interval of at least 8 hours between successive doses.

**Increasing the Dosage Above 300 mg/day:** As with other antidepressants, the full antidepressant effect of bupropion hydrochloride extended-release tablets (SR) may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 400 mg/day, given as 200 mg twice daily, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 300 mg/day.

**Maintenance Treatment:** It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. In a study in which patients with major depressive disorder, recurrent type, who had responded during 8 weeks of acute treatment with bupropion hydrochloride extended-release tablets (SR) were assigned randomly to placebo or to the same dose of bupropion hydrochloride extended-release tablets (SR) (150 mg twice daily) during 44 weeks of maintenance treatment as they had received during the acute stabilization phase, longer-term efficacy was demonstrated (see **CLINICAL TRIALS** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is unknown whether or not the dose of bupropion hydrochloride extended-release tablets (SR) needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

**Dosage Adjustment for Patients with Impaired Hepatic Function:** Bupropion hydrochloride extended-release tablets (SR) should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 100 mg every day or 150 mg every other day in these patients. Bupropion hydrochloride extended-release tablets (SR) should be used with caution in patients with hepatic impairment (including mild-to-moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild-to-moderate hepatic cirrhosis (see **CLINICAL PHARMACOLOGY**, **WARNINGS**and **PRECAUTIONS**).

**Dosage Adjustment for Patients with Impaired Renal Function:** Bupropion hydrochloride extended-release tablets (SR) should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered (see **CLINICAL PHARMACOLOGY**and **PRECAUTIONS**).

**HOW SUPPLIED**

Bupropion hydrochloride extended-release tablets USP (SR) for oral administration are available as:

**100 mg:** Aquamarine, round, biconvex, film-coated tablets, debossed “E” over “410” on one side and plain on the other side and supplied as:

NDC 0185-0410-60 bottles of 60
NDC 0185-0410-01 bottles of 100
NDC 0185-0410-52 bottles of 250
NDC 0185-0410-05 bottles of 500

**150 mg:** Plub, round, biconvex, film-coated tablets, debossed “E” over “415” on one side and plain on the other side and supplied as:

NDC 0185-0415-60 bottles of 60
NDC 0185-0415-01 bottles of 100
NDC 0185-0415-52 bottles of 250
NDC 0185-0415-05 bottles of 500
200 mg: Light pink, round, biconvex, film-coated tablets, debossed “E” on one side and debossed “1111” on the other side and supplied as:

NDC 0185-1111-60 bottles of 60
NDC 0185-1111-01 bottles of 100
NDC 0185-1111-52 bottles of 250
NDC 0185-1111-05 bottles of 500
NDC 0185-1111-10 bottles of 1000

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Store in a dry place. Keep tightly closed. Protect from light.

Dispense contents with a child-resistant closure (as required) and in a tight, light-resistant container as defined in the USP.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Do not use in combination with ZYBAN® or any other medicines that contain bupropion hydrochloride.

ZYBAN®, Wellbutrin® and Wellbutrin XL® are registered trademarks of GlaxoSmithKline.

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

Suicidality and Antidepressant Drugs

Use in Treating Psychiatric Disorders: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion hydrochloride extended-release tablets (SR) or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Bupropion hydrochloride extended-release tablets (SR) is not approved for use in pediatric patients (see WARNINGS, Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders, PRECAUTIONS, Information for Patients and PRECAUTIONS, Pediatric Use).

Use in Smoking Cessation Treatment: WELLBUTRIN®, bupropion hydrochloride extended-release tablets (SR), and WELLBUTRIN XL® are not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke.

All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the post-marketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of ZYBAN.

Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits
Medication Guide

Bupropion Hydrochloride Extended-Release Tablets (SR)

Read this Medication Guide carefully before you start using bupropion hydrochloride extended-release tablets (SR) and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about bupropion hydrochloride extended-release tablets (SR), ask your doctor or pharmacist.

IMPORTANT: Be sure to read the three sections of this Medication Guide. The first section is about the risk of suicidal thoughts and actions with antidepressant medicines; the second section is about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with medicines used to quit smoking; and the third section is entitled “What other important information should I know about bupropion hydrochloride extended-release tablets (SR)’’

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

This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member’s, healthcare provider about:

all risks and benefits of treatment with antidepressant medicines

all treatment choices for depression or other serious mental illness

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

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

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

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

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

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

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

What else do I need to know about antidepressant medicines?
• **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child’s healthcare provider for more information.

Bupropion hydrochloride extended-release tablets (SR) has not been studied in children under the age of 18 and is not approved for use in children and teenagers.

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

This section of the Medication Guide is only about the risk of changes in thinking and behavior, depression and suicidal thoughts or actions with drugs used to quit smoking.

Although bupropion hydrochloride extended-release tablets (SR) are not a treatment for quitting smoking, it contains the same active ingredient (bupropion hydrochloride) as ZYBAN® which is used to help patients quit smoking.

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

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

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

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

**What other important information should I know about bupropion hydrochloride extended-release tablets (SR)?**
Seizures: There is a chance of having a seizure (convulsion, fit) with bupropion hydrochloride extended-release tablets (SR), especially in people:

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

The chance of having seizures increases with higher doses of bupropion hydrochloride extended-release tablets (SR). For more information, see the sections “Who should not take bupropion hydrochloride extended-release tablets (SR)?” and “What should I tell my doctor before using bupropion hydrochloride extended-release tablets (SR)?” 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 bupropion hydrochloride extended-release tablets (SR) unless your doctor has said it is okay to take them.

If you have a seizure while taking bupropion hydrochloride extended-release tablets (SR), stop taking the tablets and call your doctor right away. Do not take bupropion hydrochloride extended-release tablets (SR) again if you have a seizure.

- **High blood pressure (hypertension).** Some people get high blood pressure, that can be severe, while taking bupropion hydrochloride extended-release tablets (SR). The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.
- **Severe allergic reactions.** Some people have severe allergic reaction to bupropion hydrochloride extended-release tablets (SR). Stop taking bupropion hydrochloride extended-release tablets (SR) 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 bupropion hydrochloride extended-release tablets (SR), 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.

**What is bupropion hydrochloride extended-release tablets (SR)?**

Bupropion hydrochloride extended-release tablets (SR) are a prescription medicine used to treat adults with a certain type of depression called major depressive disorder.

**Who should not take bupropion hydrochloride extended-release tablets (SR)?**

Do not take bupropion hydrochloride extended-release tablets (SR) 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 XL® Extended-Release Tablets. Bupropion is the same active ingredient that is in bupropion hydrochloride extended-release tablets (SR).
- 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 bupropion hydrochloride extended-release tablets (SR), bupropion, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in bupropion hydrochloride extended-release tablets (SR).

**What should I tell my doctor before using bupropion hydrochloride extended-release tablets (SR)?**
Tell your doctor if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See “Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions.”

- **Tell your doctor about your other medical conditions including if you:**
  - **are pregnant or plan to become pregnant.** It is not known if bupropion hydrochloride extended-release tablets (SR) can harm your unborn baby.
  - **are breastfeeding.** Bupropion hydrochloride extended-release tablets (SR) passes through your milk. It is not known if bupropion hydrochloride extended-release tablets (SR) 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 bupropion hydrochloride extended-release tablets (SR).

**How should I take bupropion hydrochloride extended-release tablets (SR)?**
- Take bupropion hydrochloride extended-release tablets (SR) exactly as prescribed by your doctor.
- **Do not chew, cut, or crush bupropion hydrochloride extended-release tablets (SR).** If you do, the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. You must swallow the tablets whole. **Tell your doctor if you cannot swallow medicine tablets.**
- Take bupropion hydrochloride extended-release tablets (SR) at the same time each day.
- Take your doses of bupropion hydrochloride extended-release tablets (SR) at least 8 hours apart.
- **You may take bupropion hydrochloride extended-release tablets (SR) 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 bupropion hydrochloride extended-release tablets (SR) can increase your chance of having a seizure.
- **If you take too much bupropion hydrochloride extended-release tablets (SR), or overdose, call your local emergency room or poison control center right away.**
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (SR) unless your doctor has told you it is okay.**
- It may take several weeks for you to feel that bupropion hydrochloride extended-release tablets (SR) is working. Once you feel better, it is important to keep taking bupropion hydrochloride extended-release tablets (SR) exactly as directed by your doctor. Call your doctor if you do not feel bupropion hydrochloride extended-release tablets (SR) is working for you.
- **Do not change your dose or stop taking bupropion hydrochloride extended-release tablets (SR) without talking with your doctor first.**

**What should I avoid while taking bupropion hydrochloride extended-release tablets (SR)?**
- **Do not drink a lot of alcohol while taking bupropion hydrochloride extended-release tablets (SR).** 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 bupropion hydrochloride extended-release tablets (SR) is working for you.**
- **Do not take any other medicines while using bupropion hydrochloride extended-release tablets (SR) unless your doctor has told you it is okay.**
- **If you take too much bupropion hydrochloride extended-release tablets (SR), or overdose, call your local emergency room or poison control center right away.**
release tablets (SR) affect you. Bupropion hydrochloride extended-release tablets (SR) can impair your ability to perform these tasks.

What are possible side effects of bupropion hydrochloride extended-release tablets (SR)?
Bupropion hydrochloride extended-release tablets (SR) can cause serious side effects. Read this entire Medication Guide for more information about these serious side effects.

The most common side effects of bupropion hydrochloride extended-release tablets (SR) are 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.

These are not all the side effects of bupropion hydrochloride extended-release tablets (SR). For a complete list, ask your doctor or pharmacist.

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

How should I store bupropion hydrochloride extended-release tablets (SR)?
- Store bupropion hydrochloride extended-release tablets (SR) at room temperature. Store out of direct sunlight. Keep bupropion hydrochloride extended-release tablets (SR) in its tightly closed bottle.
- bupropion hydrochloride extended-release tablets (SR) tablets may have an odor.

General Information about bupropion hydrochloride extended-release tablets (SR).

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use bupropion hydrochloride extended-release tablets (SR) for a condition for which it was not prescribed. Do not give bupropion hydrochloride extended-release tablets (SR) to other people, even if they have the same symptoms you have. It may harm them. Keep bupropion hydrochloride extended-release tablets (SR) out of the reach of children.

This Medication Guide summarizes important information about bupropion hydrochloride extended-release tablets (SR). For more information, talk with your doctor. You can ask your doctor or pharmacist for information about bupropion hydrochloride extended-release tablets (SR) that is written for health professionals.

What are the ingredients in bupropion hydrochloride extended-release tablets (SR)?
Active ingredient: bupropion hydrochloride.
# BUPROPION HYDROCHLORIDE EXTENDED RELEASE SR

bupropion hydrochloride tablet, film coated, extended release

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TITANIUM DIOXIDE (UNII: 15FIX9V2JP)
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)
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Labeler - Lake Erie Medical DBA Quality Care Products LLC (831276758)

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Revised: 1/2017

Lake Erie Medical DBA Quality Care Products LLC