BUPROPION HYDROCHLORIDE- bupropion hydrochloride tablet, extended release
DIRECT RX

BUPROPION HYDROCHLORIDE

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older [see WARNINGS AND PRECAUTIONS (5.1)].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [see WARNINGS AND PRECAUTIONS (5.1)].

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation [see WARNINGS AND PRECAUTIONS (5.2)].

The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although bupropion hydrochloride extended-release tablets (SR) are not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur [see WARNINGS AND PRECAUTIONS (5.2)].

Bupropion hydrochloride extended-release tablets (SR) are indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM).

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled inpatient trials and one 6-week controlled outpatient trial of adult subjects with MDD [see CLINICAL STUDIES(14)].

The efficacy of bupropion hydrochloride extended-release tablets (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 STUDIES(14)].

2.1 General Instructions for Use
To minimize the risk of seizure, increase the dose gradually [see WARNINGS AND PRECAUTIONS(5.3)]. Bupropion hydrochloride extended-release tablets (SR) should be swallowed whole and not crushed, divided, or chewed. Bupropion hydrochloride extended-release tablets (SR) may be taken with or without food.

The usual adult target dose for bupropion hydrochloride extended-release tablets (SR) is 300 mg per day, given as 150 mg twice daily. Initiate dosing with 150 mg per day given as a single daily dose in the morning. After 3 days of dosing, the dose may be increased to the 300-mg-per-day target dose, given as 150 mg twice daily. There should be an interval of at least 8 hours between successive doses. A

maximum of 400 mg per 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 per day. To avoid high peak concentrations of bupropion and/or its metabolites, do not exceed 200 mg in any single dose.

It is generally agreed that acute episodes of depression require several months or longer of antidepressant drug treatment beyond the response in the acute episode. It is unknown whether the dose of bupropion hydrochloride extended-release tablets (SR) needed for maintenance treatment is identical to the dose that provided an initial response. Periodically reassess the need for maintenance treatment and the appropriate dose for such treatment.

2.2 Dose Adjustment in Patients with Hepatic Impairment
In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of bupropion hydrochloride extended-release tablets (SR) is 100 mg per day or 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [see USE IN SPECIFIC POPULATIONS(8.7) and CLINICAL PHARMACOLOGY (12.3)].

2.3 Dose Adjustment in Patients with Renal Impairment
Consider reducing the dose and/or frequency of bupropion hydrochloride extended-release tablets (SR) in patients with renal impairment (Glomerular Filtration Rate less than 90 mL per min) [see USE IN SPECIFIC POPULATIONS (8.6) and CLINICAL PHARMACOLOGY (12.3)].

2.4 Switching a Patient to or from a Monoamine Oxidase Inhibitor (MAOI) Antidepressant
At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with bupropion hydrochloride extended-release tablets (SR). Conversely, at least 14 days should be allowed after stopping bupropion hydrochloride extended-release tablets (SR) before starting an MAOI antidepressant [see CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7.6)].

2.5 Use of Bupropion Hydrochloride Extended-Release Tablets (SR) with Reversible MAOIs Such as Linezolid or Methylene Blue
Do not start bupropion hydrochloride extended-release tablets (SR) in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions. In a patient who requires more urgent treatment of a psychiatric condition, non-pharmacological interventions, including hospitalization, should be considered [see CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7.6)].

In some cases, a patient already receiving therapy with bupropion hydrochloride extended-release tablets (SR) may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of hypertensive reactions in a particular patient, bupropion hydrochloride extended-release tablets (SR) should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with bupropion hydrochloride extended-release tablets (SR) may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue.

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg per kg with bupropion hydrochloride extended-release tablets (SR) is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use [see CONTRAINDICATIONS (4) and DRUG INTERACTIONS (7.6)].

100 mg – Aquamarine, round, biconvex, film-coated tablets, debossed “ E” over “410” on one side and plain on the other side.
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150 mg – Plum, round, biconvex, film-coated tablets, debossed “ E” over “415” on one side and plain on the other side.

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200 mg – Light pink, round, biconvex, film-coated tablets, debossed " E" on one side and debossed "1111" on the other side.

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

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Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate-release formulation of bupropion [see WARNINGS AND PRECAUTIONS (5.3)].

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Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see WARNINGS AND PRECAUTIONS (5.3) and DRUG INTERACTIONS (7.3)].

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The use of MAOIs (intended to treat psychiatric disorders) concomitantly with bupropion hydrochloride extended-release tablets (SR) or within 14 days of discontinuing treatment with bupropion hydrochloride extended-release tablets (SR) is contraindicated. There is an increased risk of hypertensive reactions when bupropion hydrochloride extended-release tablets (SR) are used concomitantly with MAOIs. The use of bupropion hydrochloride extended-release tablets (SR) within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting bupropion hydrochloride extended-release tablets (SR) in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated [see DOSAGE AND ADMINISTRATION (2.4, 2.5), WARNINGS AND PRECAUTIONS (5.4), and DRUG INTERACTIONS (7.6)].

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Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients with known hypersensitivity to bupropion or other ingredients of bupropion hydrochloride extended-release tablets (SR). Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported [see WARNINGS AND PRECAUTIONS (5.8)].

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
Patients with 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 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 (selective serotonin reuptake inhibitors [SSRIs] and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with 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 subjects. 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 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger subjects 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. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 subjects treated) are provided in Table 1.

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

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Subjects Treated
Increases Compared With Placebo	
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18 to 24	5 additional cases
Decreases Compared With Placebo	
25 to 64	1 fewer case
greater than or equal to 65	6 fewer cases

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

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

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

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

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

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for bupropion hydrochloride extended-release tablets (SR) should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

Bupropion hydrochloride extended-release tablets (SR) are not approved for smoking cessation treatment; however, ZYBAN® is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide [see BOXED WARNING and ADVERSE REACTIONS (6.2)]. Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

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

5.3 Seizure

Bupropion hydrochloride extended-release tablets (SR) can cause seizure. The risk of seizure is dose-related. The dose should not exceed 400 mg per day. Increase the dose gradually. Discontinue bupropion hydrochloride extended-release tablets (SR) and do not restart treatment if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with bupropion hydrochloride extended-release tablets (SR). Bupropion hydrochloride extended-release tablets (SR) are contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (7.3)]. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; CNS tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids); metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia); use of illicit drugs (e.g., cocaine); or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

Incidence of Seizure with Bupropion Use

When bupropion hydrochloride extended-release tablets (SR) are dosed up to 300 mg per day, the incidence of seizure is approximately 0.1% (1/1,000) and increases to approximately 0.4% (4/1,000) at the maximum recommended dose of 400 mg per day.

The risk of seizure can be reduced if the dose of bupropion hydrochloride extended-release tablets (SR) does not exceed 400 mg per day, given as 200 mg twice daily, and the titration rate is gradual.

5.4 Hypertension

Treatment with bupropion hydrochloride extended-release tablets (SR) can result in elevated blood pressure and hypertension. Assess blood pressure before initiating treatment with bupropion hydrochloride extended-release tablets (SR), and monitor periodically during treatment. The risk of hypertension is increased if bupropion hydrochloride extended-release tablets (SR) are used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity [see CONTRAINDICATIONS (4)].

Data from a comparative trial of the sustained-release formulation of bupropion HCl, 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 trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared with 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion,

NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with sustained-release bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

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

5.5 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating bupropion hydrochloride extended-release tablets (SR), screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (e.g., family history of bipolar disorder, suicide, or depression). Bupropion hydrochloride extended-release tablets (SR) are not approved for use in treating bipolar depression.

5.6 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with bupropion hydrochloride extended-release tablets (SR) have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Instruct patients to contact a healthcare professional if such reactions occur.

5.7 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion hydrochloride extended-release tablets (SR) may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.8 Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring medical treatment. In addition, there have been rare, spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue bupropion hydrochloride extended-release tablets (SR) and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

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

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

7.1 Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-Release Tablets (SR)

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (SR) and drugs that are

inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6

Ticlopidine and Clopidogrel

Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of bupropion hydrochloride extended-release tablets (SR) may be necessary when coadministered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel) [see CLINICAL PHARMACOLOGY (12.3)].

Inducers of CYP2B6

Ritonavir, Lopinavir, and Efavirenz

Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Dosage increase of bupropion hydrochloride extended-release tablets (SR) may be necessary when coadministered with ritonavir, lopinavir, or efavirenz [seeCLINICAL PHARMACOLOGY (12.3)]but should not exceed the maximum recommended dose.

Carbamazepine, Phenobarbital, Phenytoin

While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure [seeCLINICAL PHARMACOLOGY (12.3)]. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded.

7.2 Potential for Bupropion Hydrochloride Extended-Release Tablets (SR) to Affect Other Drugs
Drugs Metabolized by CYP2D6

Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, coadministration of bupropion hydrochloride extended-release tablets (SR) with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with bupropion hydrochloride extended-release tablets (SR), it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with bupropion hydrochloride extended-release tablets (SR) and such drugs may require increased doses of the drug [see CLINICAL PHARMACOLOGY (12.3)].

7.3 Drugs that Lower Seizure Threshold
Use extreme caution when coadministering bupropion hydrochloride extended-release tablets (SR) with other drugs that lower seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses and increase the dose gradually [see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.3)].

7.4 Dopaminergic Drugs (Levodopa and Amantadine)
Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Use caution when administering bupropion hydrochloride extended-release tablets (SR) concomitantly with these drugs.

7.5 Use with 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

hydrochloride extended-release tablets (SR). The consumption of alcohol during treatment with bupropion hydrochloride extended-release tablets (SR) should be minimized or avoided.

7.6 MAO Inhibitors

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of treatment with bupropion hydrochloride extended-release tablets (SR). Conversely, at least 14 days should be allowed after stopping bupropion hydrochloride extended-release tablets (SR) before starting an MAOI antidepressant [see DOSAGE AND ADMINISTRATION (2.4, 2.5) and CONTRAINDICATIONS (4)].

7.7 Drug-Laboratory Test Interactions

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

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Clinical Considerations

Consider the risks of untreated depression when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Human Data

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

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

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

Epidemiology case control study did not find increased risk for LVOTO.

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

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

Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg per m2basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg per kg per day, approximately equal to the MRHD on a mg per m2 basis) and greater. Decreased fetal weights were observed at 50 mg per kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg per kg per day (approximately 7 times the MRHD on a mg per m2basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)].

8.5 Geriatric Use

Of the approximately 6,000 subjects who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation trials), 275 were aged greater than or equal to 65 years and 47 were aged greater than or equal to 75 years. In addition, several hundred subjects aged greater than or equal to 65 years participated in clinical trials using the immediate-release formulation of bupropion (depression trials). 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.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function [see DOSAGE AND ADMINISTRATION (2.3), USE IN SPECIFIC POPULATIONS (8.6), and CLINICAL PHARMACOLOGY (12.3)].

8.6 Renal Impairment

Consider a reduced dose and/or dosing frequency of bupropion hydrochloride extended-release tablets (SR) in patients with renal impairment (Glomerular Filtration Rate: less than 90 mL per min). Bupropion

and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures [see DOSAGE AND ADMINISTRATION (2.3) and CLINICAL PHARMACOLOGY (12.3)].

8.7 Hepatic Impairment
In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of bupropion hydrochloride extended-release tablets (SR) is 100 mg per day or 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), consider reducing the dose and/or frequency of dosing [see DOSAGE AND ADMINISTRATION (2.2) and CLINICAL PHARMACOLOGY (12.3)].

9.1 Controlled Substance
Bupropion is not a controlled substance.

9.2 Abuse
Humans

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

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

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

Bupropion hydrochloride extended-release tablets (SR) are intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported when bupropion has been administered intranasally or by parenteral injection.

Animals

Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing 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.

10.1 Human Overdose Experience
Overdoses of up to 30 grams 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.

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

There are no known antidotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Induction of emesis is not recommended.

Bupropion hydrochloride extended-release tablets, USP (SR), an antidepressant of the aminoketone class, are 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-[(1,1dimethylethyl)amino]-1-propanone hydrochloride. The molecular weight is 276.2. The molecular formula is C13H18ClNO•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:

Chemical Structure
BuPROPion Hydrochloride Extended-Release Tablets, USP (SR) are supplied for oral administration as 100 mg (aquamarine), 150 mg (plum), and 200 mg (light pink), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: carnauba wax, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, hypromellose, titanium dioxide, polyethylene glycol and polysorbate. In addition, the 100 mg tablet contains FD&C blue No. 1 lake and 150 mg tablet contains FD&C red No. 40 lake and FD&C blue No. 2 lake and the 200 mg tablet contains FD&C red No. 40 lake and FD&C yellow No. 6 lake.

This product meets USP Drug Release Test #2.

12.1 Mechanism of Action
The exact mechanism of the antidepressant action of bupropion is not known, but is presumed to be related to noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase.

12.3 Pharmacokinetics
Bupropion is a racemic mixture. The pharmacological 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.

Absorption

The absolute bioavailability of bupropion hydrochloride extended-release tablets (SR) in humans has not been determined because an intravenous formulation for human use is not available. However, it appears likely that only a small proportion of any orally administered dose reaches the systemic circulation intact. In rat and dog studies, the bioavailability of bupropion ranged from 5% to 20%.

In humans, following oral administration of bupropion hydrochloride extended-release tablets (SR), peak plasma concentration (Cmax) of bupropion is usually achieved within 3 hours.

In a trial comparing chronic dosing with bupropion hydrochloride extended-release tablets (SR) 150 mg twice daily to bupropion immediate-release formulation 100 mg 3 times daily, the steady state Cmax for bupropion after bupropion hydrochloride extended-release tablets (SR) administration was approximately 85% of those achieved after bupropion immediate-release formulation administration. Exposure (AUC) to bupropion was equivalent for both formulations. Bioequivalence was also demonstrated for all three major active metabolites (i.e., hydroxybupropion, threohydrobupropion and erythrohydrobupropion) for both Cmax and AUC. 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.

Bupropion hydrochloride extended-release tablets (SR) can be taken with or without food. Bupropion Cmax and AUC were increased by 11% to 35% and 16% to 19%, respectively, when bupropion hydrochloride extended-release tablets (SR) was administered with food to healthy volunteers in three trials. The food effect is not considered clinically significant.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg per 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 are 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 CYP2B6 is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 enzymes 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 as or higher than those of bupropion.

Following a single-dose administration of bupropion hydrochloride extended-release tablets (SR) in humans, Cmax of hydroxybupropion occurs approximately 6 hours post-dose and is 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 to 450 mg per day.

Elimination

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

Renal Impairment

There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An

inter-trial comparison between normal subjects and subjects with end-stage renal failure demonstrated that the parent drug Cmax and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage renal failure. A second trial, comparing normal subjects and subjects with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL per min), showed that after a single 150-mg dose of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects with impaired renal function, while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion may be reduced by 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 USE IN SPECIFIC POPULATIONS (8.6)].

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose trials, one in subjects with alcoholic liver disease and one in subjects with mild-to-severe cirrhosis. The first trial demonstrated that the half-life of hydroxybupropion was significantly longer in 8 subjects 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 volunteers with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 groups were minimal.

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild-to-moderate hepatic cirrhosis compared with 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, Cmax, and Tmax) and its active metabolites (t½) in subjects with mild–to-moderate hepatic cirrhosis. In subjects with severe hepatic cirrhosis, significant alterations in the pharmacokinetics of bupropion and its metabolites were seen (Table 5).

Table 5. Pharmacokinetics of Bupropion and Metabolites in Patients with Severe Hepatic Cirrhosis: Ratio Relative to Healthy Matched Controls
* = Difference.

	Cmax	AUC	t½	Tmax*
Bupropion	1.69	3.12	1.43	0.5 h
Hydroxybupropion	0.31	1.28	3.88	19 h

Threo/erythrohydrobupropion amino alcohol

0.69

2.48

1.96

20 h

Left Ventricular Dysfunction

During a chronic dosing trial with bupropion in 14 depressed subjects with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), there was no apparent effect on the pharmacokinetics of bupropion or its metabolites, compared with 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 trials involving subjects dosed in a range of 300 mg per day to 750 mg per 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 trial 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 single-and multiple-dose pharmacokinetics trial suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites [see USE IN SPECIFIC POPULATIONS (8.5)].

Gender

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

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 were no statistically significant differences in Cmax, half-life, Tmax, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Drug Interactions

Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-release Tablets (SR)

In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (SR) and drugs that are inhibitors or inducers of CYP2B6. In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, fluvoxamine, and nelfinavir inhibit the hydroxylation of bupropion.

Inhibitors of CYP2B6

Ticlopidine, Clopidogrel

In a trial in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (Cmax and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine, respectively. The exposures (Cmax and AUC) of hydroxybupropion were decreased 50% and 52%, respectively, by clopidogrel, and 78% and 84%, respectively, by ticlopidine. This effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation.

Prasugrel

Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel increased bupropion Cmax and AUC values by 14% and 18%, respectively, and decreased Cmax and AUC values of hydroxybupropion, an active metabolite of bupropion, by 32% and 24%, respectively.

Cimetidine

The threohydrobupropion metabolite of bupropion does not appear to be produced by cytochrome P450 enzymes. 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 bupropion 300 mg with and without cimetidine 800 mg, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and Cmax, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

Citalopram

Citalopram did not affect the pharmacokinetics of bupropion and its three metabolites.

Inducers of CYP2B6

Ritonavir and Lopinavir

In a healthy volunteer trial, ritonavir 100 mg twice daily reduced the AUC and Cmax 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 trial, ritonavir at a dose of 600 mg twice daily decreased the AUC and the Cmax 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 trial, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and Cmax by 57%. The AUC and Cmax of hydroxybupropion were decreased by 50% and 31%, respectively.

Efavirenz

In a trial in healthy volunteers, efavirenz 600 mg once daily for 2 weeks reduced the AUC and Cmax of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, whereas Cmax of hydroxybupropion was increased by 50%.

Carbamazepine, Phenobarbital, Phenytoin

While not systematically studied, these drugs may induce the metabolism of bupropion.

Potential for Bupropion Hydrochloride Extended-release Tablets (SR) to Affect Other Drugs

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

Drugs Metabolized by CYP2D6

In vitro, bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. In a clinical trial of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYP2D6, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased the Cmax, AUC, and t1/2 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.

Citalopram

Although citalopram is not primarily metabolized by CYP2D6, in one trial bupropion increased the Cmax and AUC of citalopram by 30% and 40%, respectively.

Lamotrigine

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Lifetime carcinogenicity studies were performed in rats and mice at bupropion doses up to 300 mg per kg per day and 150 mg per kg per day, respectively. These doses are approximately 7 and 2 times the MRHD, respectively, on a mg per m2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 mg per kg per day to 300 mg per kg per day (approximately 2 to 7 times the MRHD on a mg per m2 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 assay. Bupropion produced 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 per kg per day revealed no evidence of impaired fertility.

The efficacy of the immediate-release formulation of bupropion in the treatment of major depressive disorder was established in two 4-week, placebo-controlled trials in adult inpatients with MDD (Trials 1 and 2 in Table 6) and in one 6-week, placebo-controlled trial in adult outpatients with MDD (Trial 3 in Table 6). In the first trial, the dose range of bupropion was 300 mg to 600 mg per day administered in divided doses; 78% of subjects were treated with doses of 300 mg to 450 mg per day. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion by the Hamilton Depression Rating Scale (HDRS) total score, the HDRS depressed mood item (Item 1), and the Clinical Global Impressions severity score (CGI-S). The second trial included 2 doses of the immediate-release formulation of bupropion (300 mg per day and 450 mg per day) and placebo. This trial demonstrated the effectiveness of the immediate-release formulation of bupropion, but only at the 450-mg-per-day dose. The efficacy results were significant for the HDRS total score and the CGI-S score, but not for HDRS Item 1. In the third trial, outpatients were treated with 300 mg per day of the immediate-release formulation of bupropion. This trial demonstrated the efficacy of the immediate-release formulation of bupropion as measured by the HDRS total score, the HDRS Item 1, the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S score, and the CGI-Improvement Scale (CGI-I) score.

Table 6. Efficacy of Immediate-Release Bupropion for the Treatment of Major Depressive Disorder
* Difference (drug minus placebo) in least-squares estimates with respect to the primary efficacy parameter. For Trial 1, it refers to the mean score at the endpoint visit; for Trials 2 and 3, it refers to the mean change from baseline to the endpoint visit. † Doses that are demonstrated to be statistically significantly superior to placebo.
Trial

Number

Treatment Group

Primary Efficacy Measure: HDRS

Mean Baseline Score (SD)

LS Mean Score at Endpoint Visit (SE)

Placebo-subtracted Difference*
(95% CI)
Trial 1
Immediate-Release Bupropion
300-600 mg/day†
(n = 48)
28.5 (5.1)
14.9 (1.3)
-4.7 (-8.8, -0.6)
Placebo (n = 27)
29.3 (7.0)
19.6 (1.6)
--
Mean Baseline Score (SD)
LS Mean Change from Baseline (SE)
Placebo-subtracted Difference*
(95% CI)
Trial 2
Immediate-Release Bupropion 300 mg/day
(n = 36)
32.4 (5.9)
-15.5 (1.7)
-4.1
Immediate-Release Bupropion 450 mg/day†
(n = 34)
34.8 (4.6)
-17.4 (1.7)
-5.9 (-10.5, -1.4)
Placebo (n = 39)
32.9 (5.4)
-11.5 (1.6)
--
Trial 3
Immediate-Release Bupropion 300 mg/day†
(n = 110)
26.5 (4.3)
-12.0 (NA)

-3.9 (-5.7, -1.0)

Placebo (n = 106)

27.0 (3.5)

-8.7 (NA)

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n: sample size; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval included for doses that were demonstrated to be effective; NA: not available.

Although there are not as yet independent trials demonstrating the antidepressant effectiveness of the sustained-release formulation of bupropion, trials have demonstrated the bioequivalence of the immediate-release and sustained-release forms of bupropion under steady-state conditions, i.e., bupropion sustained-release 150 mg twice daily was shown to be bioequivalent to 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 trial, outpatients meeting DSM-IV criteria for major depressive disorder, recurrent type, who had responded during an 8-week open trial on bupropion hydrochloride extended-release tablets (SR) (150 mg twice daily) were randomized to continuation of their same dose of bupropion hydrochloride extended-release tablets (SR) 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 treatment with bupropion hydrochloride extended-release tablets (SR) experienced significantly lower relapse rates over the subsequent 44 weeks compared with those receiving placebo.

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:

150 mg

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

200 mg

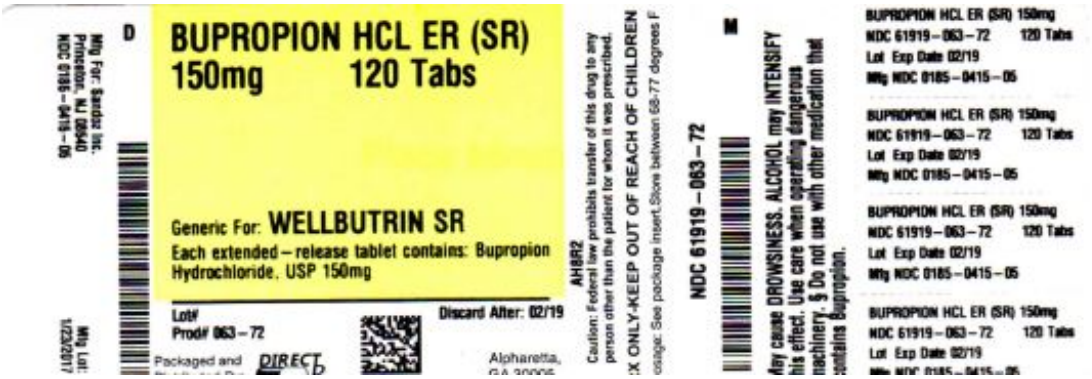
Light pink, round, biconvex, film-coated tablets, debossed “E” on one side and debossed “1111” on the other side and supplied as:

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

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

Protect from light and moisture. Keep tightly closed

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



BUPROPION HYDROCHLORIDE

bupropion hydrochloride tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-063(NDC:0185-0415)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
BUPROPION HYDROCHLORIDE (UNII: ZG7E5POY8O) (BUPROPION - UNII:01ZG3TPX31)	BUPROPION HYDROCHLORIDE	150 mg

Inactive Ingredients	
Ingredient Name	**Strength**
HYPROMELLOSES (UNII: 3NXW29V3WO)	
CARNAUBA WAX (UNII: R12CBM0EIZ)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYDROXYPROPYL CELLULOSE (TYPE H) (UNII: RFW2ET671P)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOLS (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics			
Color	purple	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	E;over;415
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**

1	NDC:61919-063-72	120 in 1 BOTTLE; Type 0: Not a Combination Product	02/16/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075932	02/16/2017	

Labeler - DIRECT RX (079254320)

Registrant - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-063)

Revised: 2/2017 DIRECT RX