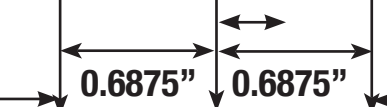


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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLETS (SR) safely and effectively. See full prescribing information for BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLETS (SR), for oral use Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

- Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants. (5.1)
Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.1)

INDICATIONS AND USAGE

- Bupropion hydrochloride extended-release tablets (SR) are an aminoketone antidepressant, indicated for the treatment of major depressive disorder (MDD). (1)
Starting dose: 150 mg/day. (2.1)
General: increase the dose and/or frequency gradually to reduce seizure risk. (2.1, 5.3)
After 3 days, may increase the dose to 300 mg/day, given as 150 mg twice daily at an interval of at least 8 hours. (2.1)
Usual target dose: 300 mg/day as 150 mg twice daily. (2.1)
Maximum dose: 400 mg/day, given as 200 mg twice daily, for patients not responding to 300 mg/day. (2.1)
Periodically reassess the dose and need for maintenance treatment. (2.1)
Moderate to severe hepatic impairment: 100 mg daily or 150 mg every other day. (2.2, 8.7)
Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.2, 8.7)
Renal impairment: Consider reducing the dose and/or frequency. (2.3, 8.6)

DOSE FORMS AND STRENGTHS

- Tablets: 100 mg, 150 mg, 200 mg. (3)
Seizure disorder. (4, 5.3)
Current or prior diagnosis of bulimia or anorexia nervosa. (4, 5.3)
Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3)
Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with bupropion hydrochloride extended-release tablets (SR) or within 14 days of stopping treatment with bupropion hydrochloride extended-release tablets (SR). (7, 4)
MAOIs intended to treat psychiatric disorders: In addition, do not start bupropion hydrochloride extended-release tablets (SR) in a patient who is being treated with linezolid or intravenous methylene blue. (4, 7.4)
Known hypersensitivity to bupropion or other ingredients of bupropion hydrochloride extended-release tablets (SR). (4, 5.8)

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
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 older adults. (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)).

INDICATIONS AND USAGE

Bupropion hydrochloride extended-release tablets (SR) is 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/day, given as 150 mg twice daily, initiate dosing with 150 mg daily given as a single daily dose in the morning. After 3 days of dosing, the dose may be increased to the 300 mg/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/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. 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 the same as 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 daily given as a single daily dose. 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), Clinical Pharmacology (12.3)).

2.3 Dose Adjustment in Patients with Renal Impairment
Consider reducing the dose and/or frequency of dosing of bupropion hydrochloride extended-release tablets (SR) in patients with renal impairment (Glomerular Filtration Rate [GFR] less than 90 mL/min). (See Use in Specific Populations (8.6), 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), 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), 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, the concurrent use of 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/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), Drug Interactions (7.6)).

3 DOSAGE FORMS AND STRENGTHS
100 mg – blue, round, biconvex, film coated tablets, debossed with "SG, 174" on one side and plain on other side.
150 mg – purple, round, biconvex, film coated tablets, debossed with "SG, 175" on one side and plain on other side.
200 mg – pink, round, biconvex, film coated tablets, debossed with "SG, 176" on one side and plain on other side.
4 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 with a current or prior diagnosis of bulimia or anorexia nervosa, or in patients with a current or prior diagnosis of bipolar disorder treated with the immediate-release formulation of bupropion. (See Warnings and Precautions (5.3)).
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), Drug Interactions (7.6)).
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), Drug Interactions (7.6)).
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)).

WARNINGS AND PRECAUTIONS

- Neuropsychiatric adverse events during smoking cessation: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.
Seizure risk: The risk is dose-related. Can minimize risk by gradually increasing the dose and limiting daily dose to 400 mg.
Hypertension: Bupropion hydrochloride extended-release tablets (SR) can increase blood pressure.
Activation of mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms.
Psychosis and other neuropsychiatric reactions: Instruct patients to contact a healthcare professional if such reactions occur.
Angle-closure glaucoma: Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants.
ADVERSE REACTIONS
Most common adverse reactions (incidence >5% and >2% more than placebo rate) are: headache, dry mouth, nausea, insomnia, dizziness, pharyngitis, constipation, agitation, anxiety, abdominal pain, tinnitus, tremor, palpitation, myalgia, sweating, itching, and anorexia.
Report SUSPECTED ADVERSE REACTIONS to Contact ScieGen Pharmaceuticals, Inc. at 1-855-724-3436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2D6 inducers: Dose increase may be necessary if coadministered with CYP2D6 inducers (e.g., ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) based on clinical response, but should not exceed the maximum recommended dose.
Drugs metabolized by CYP2D6: Bupropion inhibits CYP2D6 and can increase concentrations of antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide).
Digoxin: May decrease plasma digoxin levels.
Drugs that lower seizure threshold: Dose bupropion hydrochloride extended-release tablets (SR) with caution.
Dopaminergic drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with bupropion hydrochloride extended-release tablets (SR).
MAOIs: Increased risk of hypertensive reactions can occur when used concomitantly with bupropion hydrochloride extended-release tablets (SR).
Drug-laboratory test interactions: Bupropion hydrochloride extended-release tablets (SR) can cause false-positive urine test results for amphetamines.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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7.5 Use with Alcohol
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5 WARNINGS AND PRECAUTIONS

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 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. The 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. Table with columns: Age Range, Suicidality per 1,000 Subjects Treated, and comparison to placebo.

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 especially 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 (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 Adverse Events and Suicide Risk in Smoking Cessation Treatment
Bupropion hydrochloride extended-release tablets (SR) is not approved for smoking cessation treatment; however, it contains the same active ingredient as the smoking cessation medication ZYBAN. Serious neuropsychiatric adverse events have been reported in patients taking bupropion for smoking cessation. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. (See Adverse Reactions (6.2)). Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking bupropion who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease: some patients experienced worsening of their psychiatric illnesses. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking bupropion hydrochloride extended-release tablets and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of bupropion was reported. However, the symptoms persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

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 seizure 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), Drug Interactions (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/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/day.
The risk of seizure can be reduced if the dose of bupropion hydrochloride extended-release tablets (SR) does not exceed 400 mg/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), 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 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.

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 mania). 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 iridotomy.

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.

6 ADVERSE REACTIONS
The following adverse reactions are discussed in greater detail in other sections of the labeling:
• Suicidal thoughts and behaviors in adolescents and young adults (see Boxed Warning, Warnings and Precautions (5.1))
• Neuropsychiatric symptoms and suicide risk in smoking cessation treatment (see Warnings and Precautions (5.2))
• Seizure (see Warnings and Precautions (5.3))
• Hypertension (see Warnings and Precautions (5.4))
• Activation of mania or hypomania (see Warnings and Precautions (5.5))
• Psychosis and other neuropsychiatric reactions (see Warnings and Precautions (5.6))
• Angle-closure glaucoma (see Warnings and Precautions (5.7))
• Hypersensitivity reactions (see Warnings and Precautions (5.8))

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Adverse Reactions Leading to Discontinuation of Treatment
In placebo-controlled clinical trials, 4%, 9%, and 11% of the placebo, 300 mg/day, and 400 mg/day groups, respectively, discontinued treatment due to adverse reactions. The specific adverse reactions leading to discontinuation in at least 1% of the 300 mg/day or 400 mg/day groups and at a rate at least twice the placebo rate are listed in Table 2.

Table 2. Treatment Discontinuations Due to Adverse Reactions in Placebo-Controlled Trials. Table with columns: Adverse Reaction, Placebo (n=385), Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day (n=376), Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day (n=114).

Commonly Observed Adverse Reactions
Adverse reactions from Table 3 occurring in at least 5% of subjects 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, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Adverse reactions reported in placebo-controlled trials are presented in Table 3. Reported adverse reactions were classified using a COSTART-based Dictionary.

Table 3. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency than Placebo in Controlled Clinical Trials. Table with columns: Body System/Adverse Reaction, Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day (n=376), Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day (n=114), Placebo (n=385).

Table 3. Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency than Placebo in Controlled Clinical Trials. Detailed table with columns: Body System/Adverse Reaction, Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day (n=376), Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day (n=114), Placebo (n=385).

7.1 Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-Release Tablets (SR)
Bupropion is primarily metabolized by hydroxybupropion by CYP2D6. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (SR) and drugs that are inhibitors or inducers of CYP2D6.
Inhibitors of CYP2D6
Tolipodipine 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 CYP2D6 inhibitors (e.g., tolipodipine or clopidogrel). (See Clinical Pharmacology (12.3)).
Inducers of CYP2D6
Rifonavir, 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 rifonavir, lopinavir, or efavirenz. (See Clinical 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. (See Clinical 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 substrates of 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., lamoxifen) 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)).
Digoxin
Coadministration of bupropion hydrochloride extended-release tablets (SR) with digoxin may decrease plasma digoxin levels. (See Drug Interactions (7.4)).
7.3 Drugs that Lower Seizure Threshold
Use extreme caution when coadministering bupropion hydrochloride extended-release tablets (SR) with other

Table 4. Incidence of Weight Gain and Weight Loss (>5 lbs.) in Placebo-Controlled Trials. Table with columns: Weight Change, Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day (n=339), Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day (n=112), Placebo (n=347).

*Incidence based on the number of female subjects.
—Hypomanic adverse events occurring in greater than 0 but less than 0.5% of subjects.
Other Adverse Reactions Observed During the Clinical Development of Bupropion
In addition to the adverse reactions noted above, the following adverse reactions have been reported in clinical trials with the sustained-release formulation of bupropion in depressed subjects and in nondressed smokers, as well as in clinical trials with the immediate-release formulation of bupropion.

Adverse reaction frequencies represent the proportion of subjects who experienced a treatment-emergent adverse reaction on at least one occasion in placebo-controlled trials for depression (n = 987) or smoking cessation (n = 1,013), or subjects who experienced an adverse reaction requiring discontinuation of treatment in an open-label surveillance trial with bupropion hydrochloride extended-release tablets (SR) (n = 3,100). All treatment-emergent adverse reactions are included except those listed in Table 3, those listed in other safety-related sections of the prescribing information, those subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those not reasonably associated with the use of the drug, and those that were not serious and occurred in fewer than 2 subjects.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions are those occurring in 1/100 to 1/1,000 subjects, while rare events are defined as those occurring in fewer than 1/1,000 subjects.
Body (General): Infrequent were chills, facial edema, and photosensitivity. Rare was malaise.
Cardiovascular: Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare were syncope and myocardial infarction.

Digestive: Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue.
Hemic and Lymphatic: Infrequent was ecchymosis.
Metabolic and Nutritional: Infrequent were edema and peripheral edema.
Musculoskeletal: Infrequent were leg cramps.

Nervous System: Infrequent were abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia, hyperreflexia, hyperreflexia, hyposthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania.
Respiratory: Rare was bronchospasm.
Special Senses: Infrequent were accommodation abnormality and dry eye.
Urogenital: Infrequent were impotence, polyuria, and prostatic disorder.
Changes in Body Weight
In placebo-controlled trials, subjects experienced weight gain or weight loss as shown in Table 4.

Table 4. Incidence of Weight Gain and Weight Loss (>5 lbs.) in Placebo-Controlled Trials. Table with columns: Weight Change, Bupropion Hydrochloride Extended-Release Tablets (SR) 300 mg/day (n=339), Bupropion Hydrochloride Extended-Release Tablets (SR) 400 mg/day (n=112), Placebo (n=347).

In clinical trials conducted with the immediate-release formulation of bupropion, 35% of subjects receiving tricyclic antidepressants gained weight, compared with 9% of subjects treated with the immediate-release formulation of bupropion. Weight gain was a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of bupropion hydrochloride extended-release tablets (SR) should be considered.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of bupropion hydrochloride extended-release tablets (SR) and are not described elsewhere in the label. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Body (General)
Headache, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness. (See Warnings and Precautions (5.8)).
Cardiovascular
Complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe), plebitis, polymyositis embolism, and Brugada pattern syndrome.
Digestive
Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, pancreatitis, and stomach ulcer.
Endocrine
Hypoglycemia, hypoglycemia, hypонатremia, and syndrome of inappropriate antidiuretic hormone secretion.

Hemic and Lymphatic
Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.
Metabolic and Nutritional
Musculoskeletal
Muscle rigidity/fever/rhabdomyolysis and muscle weakness.
Nervous System
Abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, completed suicide, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome (dyskinesia, dystonia, hypokinesia, parkinsonism), hallucinations, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, unmasking tardive dyskinesia, and aseptic meningitis.

Respiratory
Pneumonia
Skin and Subcutaneous Tissue Disorders
Alopecia, angioedema, exfoliative dermatitis, hirsutism, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms (DRESS).
Social Senses
Deafness, increased intraocular pressure, and mydriasis.
Urogenital
Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecostasia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

7 DRUG INTERACTIONS
7.1 Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-Release Tablets (SR)
Bupropion is primarily metabolized by hydroxybupropion by CYP2D6. Therefore, the potential exists for drug interactions between bupropion hydrochloride extended-release tablets (SR) and drugs that are inhibitors or inducers of CYP2D6.
Inhibitors of CYP2D6
Tolipodipine 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 CYP2D6 inhibitors (e.g., tolipodipine or clopidogrel). (See Clinical Pharmacology (12.3)).
Inducers of CYP2D6
Rifonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease b

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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), *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 hypersensitive 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 *Drug Interactions* (2.4, 2.5), *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 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester have not identified an increased risk of congenital malformations overall [see *Data*]. There are risks to the mother associated with untreated depression in pregnancy [see *Clinical Considerations*]. When bupropion was administered to pregnant rats during organogenesis, there was no evidence of fetal malformations at doses up to approximately 11 times the maximum recommended human dose (MRHD) of 400 mg/day. When given to pregnant rabbits during organogenesis, non-dose-related increases in incidence of fetal malformations, and skeletal variations were observed at doses approximately equal to the MRHD and lower. Decreased fetal weights were seen at doses twice the MRHD and greater [see *Animal Data*].

The estimated background risk of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and of miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants during pregnancy at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience postpartum major depressive disorder than women who continued antidepressants. Consider the risks to the mother of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum.

Data

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. The Registry was not designed or powered to evaluate specific defects but suggested a possible increase in cardiac malformations.

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, which had a limited number of exposed cases with cardiovascular malformations, and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) of self-reported bupropion use from the National Birth Defects Prevention Study (NBDS) 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 NBDS found increased risk for LVOTO ($n = 10$; adjusted OR = 2.6, 95% CI: 1.2, 5.7), and the Stone 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 Stone 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 NBDS 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 in case control studies.

Animal Data: In studies conducted in pregnant rats and rabbits, bupropion was administered orally during the period of organogenesis at 150 and 300 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m² basis). There was no evidence of fetal malformations in rats. When given to pregnant rabbits during organogenesis, non-dose-related increases in incidence of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day; approximately equal to the MRHD on a mg/m² basis) and greater. Decreased fetal weights were observed at doses of 50 mg/kg/day (approximately 2 times the MRHD on a mg/m² basis) and greater. No maternal toxicity was evident at doses of 50 mg/kg/day or less. In a pre- and postnatal developmental study, bupropion administered orally to pregnant rats at doses of up to 150 mg/kg/day (approximately 4 times the MRHD on a mg/m² basis) from embryonic implantation through lactation had no effect on pup growth or development.

8.2 Lactation

Risk Summary

Data from published literature report the presence of bupropion and its metabolites in human milk [see *Data*]. There are no data on the effects of bupropion or its metabolites on milk production. Limited data from postmarketing reports have not identified a clear association of adverse reactions in the breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bupropion hydrochloride extended-release tablets (SR) and any potential adverse effects on the breastfed child from bupropion hydrochloride extended-release tablets (SR) or from the underlying maternal condition.

Data

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/kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Postmarketing reports have described seizures in breastfed infants. The relationship of bupropion exposure and these seizures is unclear.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [see *Boxed Warning, 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 ≥65 years and 47 were aged ≥75 years. In addition, several hundred subjects aged ≥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), *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 (GFR 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), *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), *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

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-Benzendrine 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 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 psychotropic 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 psychotropic drugs.

10 OVERDOSAGE

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, mental status changes, sinus tachycardia, ECG changes such as conduction disturbances (including QRS prolongation) or arrhythmias, clonus, myoclonus, and hyperreflexia. 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.

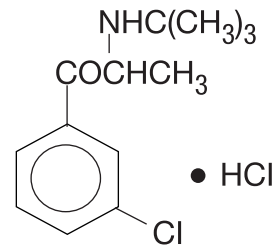
10.2 Overdosage Management

Consult a Certified Poison Control Center for up-to-date guidance and advice. Call 1-800-222-1222 or refer to www.poisn.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.

11 DESCRIPTION

Bupropion hydrochloride extended-release tablets, USP (SR), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (+)-1-(3-(4-chlorophenyl)-2-(1-(1-(dimethylamino)ethyl)propanoate hydrochloride). The molecular weight is 276.2. The molecular formula is C₁₇H₁₉ClNOHCl. Bupropion hydrochloride powder is white, powder, soluble in 1:10 HCl, alcohol 36%, and in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



Bupropion hydrochloride extended-release tablets, USP (SR), are supplied for oral administration as 100 mg (blue), 150 mg (purple), and 200 mg (pink), film-coated, extended-release tablets. Each tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: copovidone, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. In addition, the 100 mg tablet contains FD&C Blue No. 1 Brilliant Blue FCF Aluminum Lake, the 150 mg tablet contains FD&C Blue No. 2 Orange Carmine Aluminum Lake and FD&C Red No. 40 Allura Red AC Aluminum Lake, and the 200 mg tablet contains FD&C Red No. 40 Allura Red AC Aluminum Lake. In addition, flavoring agent contains dextrose, ethyl alcohol, gum arabic, propylene glycol and silicon dioxide.

Bupropion hydrochloride extended-release tablets, USP (SR) meets USP *Dissolution* Test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of the antidepressant action of bupropion is not known, but is presumed to be related to noreadrenergic 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.

12.2 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.

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 (C_{max}) 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 150 mg 3 times daily, the steady state C_{max} 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 C_{max} 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 C_{max} 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.

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mg/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.

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 CYP2D6 is the major enzyme involved in the formation of threohydrobupropion. Oxidation of the propionide 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, C_{max} 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 time course of plasma concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination half-lives are longer, 33 (±10) and 37 (±13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

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

Specific Populations

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.

Patients with 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 C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2- 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/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 threohydrobupropion (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)].

Patients with 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 AUC for hydroxybupropion was 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, C_{max}, and T_{max}) and its active metabolites (t_{1/2}) 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

	C _{max}	AUC	t _{1/2}	T _{max} ^a
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

^a Difference.

Patients with 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 to 750 mg/day, at 3 times-daily dosing, showed a weak 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 pharmacokinetic trial suggested that there may be an increased risk for accumulation of bupropion and its metabolites [see *Use in Specific Populations* (8.5)].

Male and Female Patients: 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 C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

Drug Interaction Studies

Potential for Other Drugs to Affect Bupropion Hydrochloride Extended-Release Tablets (SR): In vitro studies indicate that bupropion is primarily metabolized by hydroxybupropion by CYP2B6. There are no known clinically important 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 nefazodone inhibit the hydroxylation of bupropion.

Inhibitors of CYP2D6: *Ticlopidine, Clopidogrel* In a trial in healthy male volunteers, clopidogrel 75 mg once daily or ticlopidine 250 mg twice daily increased exposures (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, and by 38% and 85% for ticlopidine, respectively. The exposures (C_{max} 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.

Propranolol: Propranolol is a weak inhibitor of CYP2B6. In healthy subjects, propranolol increased bupropion C_{max} and AUC values by 14% and 18%, respectively, and decreased C_{min} 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 concurrent 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 C_{max}, respectively, of the combined bupropion and hydroxybupropion.

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

Inducers of CYP2B6: *Rifampin* and *Lopinavir*: In a healthy volunteer trial, rifampin 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23% by the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

In a second healthy volunteer trial, rifampin at a dose of 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%. The exposure of hydroxybupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%. In another healthy volunteer trial, lopinavir 400 mg/rifampin 100 mg twice daily decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion were decreased by 50% and 31%, respectively.

Flavoxate: In a trial in healthy volunteers, flavoxate 600 mg once daily for 2 weeks reduced the AUC and C_{max} of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged, whereas the AUC of threohydrobupropion was increased 50%.

Carbamazepine, Phenytoin, 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

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/day followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and t_{1/2} of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was more pronounced in subjects who were poor metabolizers of CYP2D6. 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 nose marrow cytogenetic studies.

There were no effects on male and female fertility when rats were administered oral doses of bupropion up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m² basis) to females prior to mating and either through Day 19 of gestation or through lactation and to males for 60 days prior to and through mating. However, doses of 200 mg/kg/day (approximately 5 times the MRHD on a mg/m² basis) or greater, caused transient ataxia or behavioral changes in adult female rats. There were also no adverse effects on fertility, reproduction, or growth and development of male or female offspring.

14 CLINICAL STUDIES

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 two 8-week, placebo-controlled trials 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 administered in divided doses; 78% of subjects were treated with doses of 300 mg to 450 mg/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 (