HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use APLENZIN® safely and effectively. See full prescribing information for APLENZIN.

APLENZIN® (bupropion hydrobromide) extended-release tablets for oral use

Initial U.S. Approval: 1985

WARNING: SUICIDALITY AND ANTidepressANT DRUGS AND NEUropsychiatric REACTIONS In patients-taking bupropion for smoking cessation

See full prescribing information for complete boxed warning.

- Antidepressants increased the risk of suicidal behavior and thoughts in children, adolescents, and young adults treated for major depressive disorder (MDD) and other psychiatric disorders. Monitor closely for clinical worsening and suicidal behavior. (5.1)
- Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation. (5.2)

RECENT MAJOR CHANGES

Warnings and Precautions (5.7) 07/2014

INDICATIONS AND USAGE

APLENZIN is an aminoketone antidepressant, indicated for the treatment of major depressive disorder (MDD) and seasonal affective disorder (SAD). Periodically reevaluate long-term usefulness for the individual patient. (1)

DOSAGE AND ADMINISTRATION

General: Increase dose gradually to reduce seizure risk. (2.1, 5.3)

Major Depressive Disorder
- Starting dose: 174 mg once daily (equivalent to 150 mg bupropion HCl). Usual target dose: 348 mg once daily (equivalent to 300 mg bupropion HCl). (2.3)
- After 4 days, may increase the dose to 348 mg once daily. (2.3)

Seasonal Affective Disorder
- Initiative treatment in the autumn prior to onset of seasonal depressive symptoms. (2.4)
- Starting dose: 174 mg once daily (equivalent to 150 mg bupropion HCl). Usual target dose: 348 mg once daily (equivalent to 300 mg bupropion HCl). (2.4)
- After one week, may increase the dose to 348 mg once daily. (2.4)
- Continue treatment through the winter season. (2.4)
- Severe Hepatic Impairment
- Maximum dose 174 mg every other day. (2.6)

DOSAGE FORMS AND STRENGTHS

- Extended-release tablets: 174 mg, 348 mg, 522 mg (3)

CONTRAINDICATIONS

- Seizure disorder or conditions that increase the risk of seizure (e.g., bulimia or anorexia nervosa, abrupt discontinuation of alcohol, benzodiazepines, antiepileptics, sedative/hypnotics, barbiturates. (4, 5.3)
- MAO inhibitors: discontinue MAOI at least 2 weeks prior to bupropion use. (4)
- Known hypersensitivity to bupropion or other ingredients of APLENZIN. (4, 5.7)

WARNINGs AND PRECAUTIONS

- Seizure risk: The risk is dose-related. Can minimize risk by limiting daily dose to 522 mg and gradually increasing the dose. Discontinue if seizure occurs. (4, 5.3, 7.3)
- Hypertension: APLENZIN can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment. (5.4)
- Activation of psychosis, mania/hypomania: Screen patients for bipolar disorder and monitor for these symptoms. (5.5)
- Psychosis and other neuropsychiatric reactions. Discontinue if psychosis or neuropsychiatric reactions occur. (5.6)
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.7)

ADVERSE REACTIONS

Most common adverse reactions are (incidence ≥5%; ≥2x placebo rate): dry mouth, nausea, insomnia, dizziness, pharyngitis, abdominal pain, agitation, anxiety, tremor, palpitation, sweating, tinnitus, myalgia, anorexia, urinary frequency, rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-877-361-2719 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- CYP2B6 inhibitors and inducers: APLENZIN is primarily metabolized by CYP2B6. Dose adjustment may be necessary if coadministered with CYP2B6 inhibitors or inducers. Inhibitors (e.g., lortatidine and clobopride) can increase levels of bupropion. Inducers (rifampin, lovafenapin, and efavirenz) can decrease levels of bupropion. (7.1)
- Carbamazepine, phenobarbital, phenytoin can induce metabolism of APLENZIN and decrease exposure. Dose increase may be necessary. (7.1)
- Drugs metabolized by CYP2B6: Bupropion inhibits CYP2B6 and can increase concentrations of antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics. (e.g., propafenone, flecainide). Consider dose reduction when using with bupropion. (7.2)
- Drugs that lower seizure threshold: Cautious bupropion dosing (5.3, 7.3)
- Dopaminergic Drugs (levodopa and amantadine): CNS toxicity can occur when used concomitantly with APLENZIN. (7.4)
- Drug laboratory test interactions: APLENZIN can cause false-positive urine test results for amphetamine. (7.6)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if benefit outweighs potential risk to the fetus. (8.1)
- Nursing: Bupropion and its metabolites are present in human milk. Exercise caution when APLENZIN is administered to a nursing mother. (8.3)
- Mild-to-moderate hepatic impairment: Consider reducing the dose and/or frequency of dosing. (8.7)
- Renal impairment: Consider reducing the dose and/or frequency. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide

Revised: 07/2014

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FULL PRESCRIBING INFORMATION
APLENZIN® (bupropion hydrobromide) Extended-Release Tablets

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS AND NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thoughts or behavior (suicidality) in children, adolescents, and young adults in short-term trials of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of APLENZIN or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo; however, suicides were uncommonly reported in placebo groups in these studies. It is unknown whether suici
dality risk returns to baseline after discontinuation. APLENZIN is not approved for smoking cessation; 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. Some of the cases occurred in patients taking bupropion who continued to smoke. Although APLENZIN is 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)].

1 INDICATIONS AND USAGE
1.1 Major Depressive Disorder

APLENZIN® (bupropion hydrobromide extended-release tablets) is indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM). The efficacy of the immediate-release formulation of bupropion was established in two 4-week controlled clinical trials and one 6-week controlled outpatient trial of adult patients with MDD. The efficacy of the sustained-release formulation of bupropion in the maintenance treatment of MDD was established in a long-term (up to 44 weeks), placebo-controlled trial in patients who had responded to bupropion in an 8-week study of acute treatment [see Clinical Studies (14.1)].

1.2 Seasonal Affective Disorder

APLENZIN is indicated for the prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder (SAD). The efficacy of bupropion hydrochloride extended-release tablets in the prevention of seasonal major depressive episodes was established in 3 placebo-controlled trials in adult outpatients with a history of MDD with an autumn-winter seasonal pattern as defined in the DSM [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

To minimize the risk of seizure, increase the dose gradually [see Warnings and Precautions (5.3)]. APLENZIN should be swallowed whole and not crushed, divided, or chewed. The recommended starting dose for SAD is 174 mg once daily. After 7 days of dosing, the dose may be increased to the target dose of 348 mg once daily in the morning. Doses above 300 mg of bupropion HCl extended-release (equivalent to APLENZIN 348 mg) were not assessed in the SAD trials.

For the prevention of seasonal MDD episodes associated with SAD, initiate APLENZIN in the autumn, prior to the onset of depressive symptoms. Continue treatment through the winter season. Taper and discontinue APLENZIN in early spring. For patients treated with 348 mg per day, decrease the dose to 150 mg once daily before discontinuing APLENZIN. Individualize the timing of initiation and duration of treatment should be individualized, based on the patient’s historical pattern of seasonal MDD episodes.

2.2 Dose for Major Depressive Disorder (MDD)

The recommended starting dose for MDD is 174 mg once daily in the morning. After 4 days of dosing, the dose may be increased to the target dose of 348 mg once daily in the morning. It is generally agreed that acute episodes of depression require several months or longer of antidepressant treatment beyond the response in the acute episode. It is unknown whether the APLENZIN dose 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.

2.4 Dosage for Seasonal Affective Disorder (SAD)

The recommended starting dose for SAD is 174 mg once daily. After 7 days of dosing, the dose may be increased to the target dose of 348 mg once daily in the morning. Doses above 300 mg of bupropion HCl extended-release (equivalent to APLENZIN 348 mg) were not assessed in the SAD trials.

For the prevention of seasonal MDD episodes associated with SAD, initiate APLENZIN in the autumn, prior to the onset of depressive symptoms. Continue treatment through the winter season. Taper and discontinue APLENZIN in early spring. For patients treated with 348 mg per day, decrease the dose to 150 mg once daily before discontinuing APLENZIN. Individualize the timing of initiation and duration of treatment should be individualized, based on the patient’s historical pattern of seasonal MDD episodes.

2.5 To Discontinue APLENZIN, Taper the Dose

When discontinuing treatment in patients treated with APLENZIN 348 mg once daily, decrease the dose to 174 mg once daily prior to discontinuation.

2.6 Dosage Adjustment for Patients with Impaired Hepatic Function

For patients with severe hepatic impairment, the recommended initial and maximum dose is 174 mg every other day [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

APLENZIN Extended-Release Tablets, 174 mg of bupropion hydrobromide, are white to off-white, round tablets printed with “BR” over “174”. APLENZIN Extended-Release Tablets, 348 mg of bupropion hydrobromide, are white to off-white, round tablets printed with “BR” over “348”.

APLENZIN Extended-Release Tablets, 522 mg of bupropion hydrobromide, are white to off-white, round tablets printed with “BR” over “522”.

4 CONTRAINDICATIONS

APLENZIN is contraindicated in patients with the following conditions:

- Seizure disorder or conditions that increase the risk of seizures (e.g., arteriovenous malformation, severe head injury, CNS tumor or CNS infection, severe stroke, anorexia nervosa or bulimia, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiplatelet drugs [see Warnings and Precautions (5.3)].
- Known hypersensitivity to bupropion. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported [see Warnings and Precautions (5.3)].
- Concurrent use of monoamine oxidase (MAO) inhibitor, because MAOIs have the potential to enhance central nervous (CNS) toxicity. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with APLENZIN.

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidal ideation in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (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 major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults aged beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 256 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2.

Table 2: Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18 years</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>18-24 years</td>
<td>5 additional cases</td>
</tr>
<tr>
<td>≥25-64 years</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>≥65 years</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>
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 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 and Use in Specific Populations (8.4)].

The following symptoms, anorexia, agitation, panic anxiety, delusions, hallucinations, hostility, irritability, impulsivity, anxiety, 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 an actual link between the emergence of such symptoms and the worsening of depression and/or the emergence of suicidal ideation has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

The incidence of seizure with APLENZIN has not been formally evaluated in clinical trials. In studies using bupropion HCl sustained-release up to 300 mg per day (equivalent to APLENZIN 348 mg per day) and 400 mg per day (equivalent to APLENZIN 464 mg per day) [see Clinical Trials Experience section] the incidence of seizure was approximately 0.4% (13/3200) with bupropion HCl extended-release (equivalent to APLENZIN 464 mg/day). In a large prospective, follow-up study, the incidence was approximately 0.4% (13/3200) with bupropion HCl immediate-release in the range of 300 mg to 450 mg per day (equivalent to APLENZIN 348 mg t o 522 mg per day).

Additional data accumulated for bupropion immediate-release suggests that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day (equivalent to APLENZIN 522 mg and 696 mg per day). The risk of seizure can be reduced if the APLENZIN dose does not exceed 522 mg per day. The mean daily dose was 270 mg per day. The mean duration of bupropion exposure was 126 days.

In a study of bupropion immediate-release in MDD patients with stable congestive heart failure (N=36), the risk of stroke, anorexia nervosa or bulimia, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see Contraindications (4)]. The following conditions can also increase the risk of seizure: concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antidepressants, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic disorders (e.g., hypoglycemia, hypotension, severe hepatic impairment, and hypoxia), or use of illicit drugs (e.g., cocaine) or abuse or misuse of prescription drugs such as CNS depressants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin, use of anorectic drugs, excessive alcohol abuse, alcohol, benzodiazepines, sedative/hypnotics, or opiates. Incidence of Seizure with Bupropion Use

Adverse Reactions Occurring at an Incidence of 1% or More in Patients Treated with Bupropion HCl Sustained-Release 400 mg/day and Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction Term</th>
<th>Placebo (n=385)</th>
<th>Bupropion HCl Sustained-Release 300 mg/day (n=276)</th>
<th>Bupropion HCl Sustained-Release 400 mg/day1 (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>0.0%</td>
<td>2.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3%</td>
<td>0.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.3%</td>
<td>0.0%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Equivalent to 348 mg/day bupropion HBr

†Equivalent to 464 mg/day bupropion HBr

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

Adverse Reactions Occurring at an Incidence of ≥1% in Patients Treated with Bupropion HCl Immediate-Release

Table 4 summarizes the adverse reactions that occurred in placebo-controlled trials in patients treated with bupropion HCl sustained-release 300 mg/day and 400 mg/day. These include reactions that occurred in either the 300 mg or 400 mg group at an incidence of 1% or more and were more frequent than in the placebo group are included.

Table 3: Treatment Discontinuation Due to Adverse Reactions in Placebo-Controlled Trials in MDD

<table>
<thead>
<tr>
<th>Adverse Reaction Term</th>
<th>Placebo (n=385)</th>
<th>Bupropion HCl Sustained-Release 300 mg/day (n=276)</th>
<th>Bupropion HCl Sustained-Release 400 mg/day1 (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>0.0%</td>
<td>2.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.3%</td>
<td>0.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Agitation</td>
<td>0.3%</td>
<td>0.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Migraine</td>
<td>0.3%</td>
<td>0.0%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

Equivalent to 348 mg/day bupropion HBr

†Equivalent to 464 mg/day bupropion HBr

In clinical trials with bupropion HCl immediate-release, 10% of patients and volunteers discontinued due to an adverse reaction. Reactions resulting in discontinuation, (in addition to those listed above for the sustained-release formulation), included vomiting, seizures, and sleep disturbances.
<table>
<thead>
<tr>
<th>Body System/Adverse Reaction</th>
<th>Placebo (n=385)</th>
<th>Bupropion HCI Sustained-Release 300 mg/day (n=376) *</th>
<th>Bupropion HCI Sustained-Release 400 mg/day † (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body (General)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>23%</td>
<td>26%</td>
<td>25%</td>
</tr>
<tr>
<td>Infection</td>
<td>6%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>1%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Pain</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Fever</td>
<td>—</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>2%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Flushing</td>
<td>—</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Migraine</td>
<td>1%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7%</td>
<td>17%</td>
<td>24%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>3%</td>
<td>2%</td>
<td>6%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Arthritis</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Twitch</td>
<td>—</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>11%</td>
<td>16%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>Agitation</td>
<td>2%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Tremor</td>
<td>1%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>3%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Irritability</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Memory decreased</td>
<td>1%</td>
<td>—</td>
<td>3%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Central nervous system stimulation</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Increased cough</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>2%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Rash</td>
<td>1%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>2%</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Equivalent to 348 mg/day bupropion HBr
†Equivalent to 464 mg/day bupropion HBr
‡Incidence based on the number of female patients.
—Hyphen denotes adverse reactions occurring in greater than 0 but less than 0.5% of patients.

The following additional adverse reactions occurred in controlled trials of bupropion HCl immediate-release (300 to 600 mg per day) at an incidence of at least 1% more frequently than in the placebo group were: cardiac arrhythmia (5% vs. 4%), hypertention (4% vs. 2%), hypotension (3% vs. 2%), tachycardia (11% vs. 9%), appetite increased (4% vs. 2%), dypsnea (3% vs. 2%), menstrual complaints (5% vs. 1%), akathisia (2% vs. 1%), impaired sleep quality (4% vs. 2%), sensory disturbance (4% vs. 3%), confusion (8% vs. 5%), decreased libido (3% vs. 2%), hostility (6% vs. 4%), auditory disturbance (5% vs. 3%), and gustatory disturbance (3% vs. 1%).

Seasonal Affective Disorder

In placebo-controlled clinical trials in SAD, 9% of patients treated with bupropion HCl extended-release and 5% of patients treated with placebo discontinued treatment because of adverse reactions. The adverse reactions leading to discontinuation in at least 1% of patients treated with bupropion and at a rate numerically greater than the placebo rate were insomnia (2% vs. <1%) and headache (1% vs. <1%).

Table 5 summarizes the adverse reactions that occurred in patients treated with bupropion HCl extended-release for up to approximately 6 months in 3 placebo-controlled trials. These include reactions that occurred at an incidence of 2% or more and were more frequent than in the placebo group.

Table 5: Adverse Reactions in Placebo-Controlled Trials in Patients with SAD

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Placebo (n=511)</th>
<th>Bupropion HCI Extended-Release (n=537)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>15%</td>
<td>26%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2%</td>
<td>9%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>34%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Tremor</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Agitation</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Table 5: Adverse Reactions in Placebo-Controlled Trials in Patients with SAD (continued)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>Placebo (n=511)</th>
<th>Bupropion HCl Extended-Release (n=537)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling jitter</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>&lt;1%</td>
<td>3%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Changes in Body Weight

Table 6 presents the incidence of body weight changes (≥5 lbs) in the short-term MDD trials using bupropion HCl extended-release. There was a dose-related decrease in body weight.

Table 6: Incidence of Weight Gain or Weight Loss (≥5 lbs) in MDD Trials Using Bupropion HCl Extended-Release

<table>
<thead>
<tr>
<th>Weight Change</th>
<th>Bupropion HCl Extended-Release 300 mg/day (n=339)</th>
<th>Bupropion HCl Extended-Release 400 mg/day (n=112)</th>
<th>Placebo (n=347)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gained &gt;5 lbs</td>
<td>3%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Lost &gt;5 lbs</td>
<td>14%</td>
<td>19%</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Equivalent to 348 mg/day bupropion HBr
†Equivalent to 464 mg/day bupropion HBr

Table 7 presents the incidence of body weight changes (≥5 lbs) in the 3 SAD trials using bupropion HCl extended-release. A higher proportion of subjects in the bupropion group (23%) had a weight loss >5 lbs., compared to the placebo group (11%). These were relatively long-term trials (up to 6 months).

Table 7: Incidence of Weight Gain or Weight Loss (≥5 lbs) in SAD Trials Using Bupropion HCl Extended-Release

<table>
<thead>
<tr>
<th>Weight Change</th>
<th>Bupropion HCl Extended-Release 150 to 300 mg/day (n=537)</th>
<th>Placebo (n=511)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gained &gt;5 lbs</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td>Lost &gt;5 lbs</td>
<td>23%</td>
<td>11%</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of APLENZIN. 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)

Chills, facial edema, edema, peripheral edema, musculoskeletal chest pain, photosensitivity, and malaise.

Cardiovascular

Postural hypotension, stroke, vasodilation, syncope, complete atrioventricular block, extrasystoles, myocardial infarction, phlebitis, and pulmonary embolism.

Dermatologic

Abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, thirst, edema of tongue, cuticle, exophtalmos, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer.

Endocrine

Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone secretion.

Hemic and Lymphatic

Eosinophilia, anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

Metabolic and Nutritional

Glycosuria.

Musculoskeletal

Leg cramps, fever/rhabdomyolysis, and muscle weakness.

Nervous System

Abnormal coordination, depersonalization, emotional lability, hyperkinesia, hypotonia, hypotonia, vertigo, amnesia, ataxia, derealization, abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, neuragia, neuropsychopathic ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory

Bronchoconstriction and pneumonia.

Skin

Maculopapular rash, alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses

Accommodation abnormality, dry eye, deafness, increased intraocular pressure, angle-closure glaucoma, and mydriasis.

Urogenital

Impotence, polycystic ovary syndrome, prostate disorder, abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomasia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis.

7. Drug Interactions

7.1 Potential for Other Drugs to Affect APLENZIN

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between APLENZIN and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6

Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposure. Dosage reduction of APLENZIN may be necessary when coadministered with ticlopidine or clopidogrel [see Clinical Pharmacology (12.3)].

Inducers of CYP2B6

Ritonavir, Lopinavir, and Elavirenz: Concomitant treatment with these drugs can decrease bupropion exposure. Dosage increase of APLENZIN may be necessary when coadministered with ritonavir, lopinavir, or elavirenz [see Clinical Pharmacology (12.3)].

Other CYP Inducers

Carbamazepine, Phenoobarbital, Phenytoin: Concomitant treatment with these drugs can decrease bupropion exposure. It may be necessary to increase the dose of APLENZIN when coadministered with carbamazepine, phenobarbital, or phenytoin [see Clinical Pharmacology (12.3)].

In addition, studies suggest that particular sertraline, paroxetine, fluoxetine, and nefazodone inhibit the hydroxylation of bupropion and may increase bupropion exposure.

7.2 Potential for APLENZIN to Affect Other Drugs

Drugs Metabolized by CYP2D6

Bupropion and hydroxybupropion are CYP2D6 inhibitors. Therefore, coadministration of APLENZIN 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, and thioridazine), beta-blockers (e.g., metoprolol, and atenolol), and type 1C antiarrhythmics (e.g., propafenone, flecainide). When used concomitantly with APLENZIN 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 APLENZIN 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 APLENZIN with other drugs that lower the seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Use low initial doses of APLENZIN and increase the dose gradually [see 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 APLENZIN concomitantly with these drugs.

7.5 MAO Inhibitors

Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine [see Contraindications (4)].

7.6 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

Pregnancy Category C

Risk Summary

Data from epidemiological studies including pregnant women indicate no increased risk of congenital malformations with APLENZIN exposure in pregnancy. Data regarding the risk of congenital cardiovascular malformations with first trimester bupropion exposure is inconsistent. No clear evidence of teratogenicity was observed in reproductive developmental studies conducted in rats and rabbits. However, in rabbits, slightly increased incidences 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 and decreased fetal weights were seen at 50 mg/kg and greater. APLENZIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Consider the risk of untreated depression when discontinuing or changing treatment with antidepressants during pregnancy and postpartum.

Human Data

Data from a retrospective cohort study using the United Healthcare database (1213 infants exposed to bupropion in the first trimester) demonstrated no greater risk for congenital malformations overall or cardiovascular malformations specifically after first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or to bupropion exposure outside of the first trimester.
A retrospective case-controlled study included 6853 infants with cardiac defects and 5753 with noncardiac defects from the National Birth Defects Prevention Study. This study found an association between infants with left outflow tract defects (LVOTO) with maternal bupropion use but not among infants with other types of heart defects or six other noncardiac defect categories. A subsequent reanalysis of the United Healthcare database, to assess the risk of cardiovascular malformations, particularly LVOTO, lacked adequate power to detect an increased risk.

### Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m² basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, increased incidences of fetal deaths 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 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m² basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

### 8.2 Labor and Delivery

The effect of APLENZIN tablets on labor and delivery in humans is unknown.

### 8.3 Nursing Mothers

Bupropion and its metabolites are present in human milk. In a lactation study of ten 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. Exercise caution when APLENZIN is administered to a nursing woman.

### 8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established. When considering the use of APLENZIN in a child or adolescent, balance the potential risks with the clinical need [see Boxed Warning and Warnings and Precautions (5.1)].

### 8.5 Geriatric Use

Of the approximately 6000 patients who participated in clinical trials with bupropion hydrochloride sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. In addition, several hundred patients ≥65 years of age participated in clinical trials using the immediate-release formulation of bupropion hydrochloride (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Reported clinical experience has not identified differences in responses between the elderly and younger patients. However, geriatric 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 (2.5, 2.6), Use in Specific Populations (8.6, 8.7), and Clinical Pharmacology (12.3)].

### 8.6 Renal Impairment

APLENZIN should be used with caution in patients with renal impairment. Consider a reduced dose and/or frequency of dosing, because bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse reactions that could indicate high drug or metabolite levels. Monitor closely for adverse reactions that could indicate high bupropion or metabolite exposures [see Clinical Pharmacology (12.3)].

### 8.7 Hepatic Impairment

For patients with severe hepatic impairment, the maximum APLENZIN dose is 174 mg every other day. In patients with mild to moderate impairment, consider reducing the dose and/or frequency of dosing [see Dosage and Administration (2.6) and 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 studies of bupropion HCl immediate-release conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients demonstrated an increase in motor activity and agitation/excitement.

In a population of individuals experienced with drugs of abuse, a single dose of 400 mg bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and local subjective effects. Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (that could not be tested because of the risk of seizure) might be modestly attractive to those who abuse CNS stimulant drugs.

### Animals

Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has shown to increase locomotor activity, elicit a mild amphetamine-like effect, and produce a mild rage response. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and methamphetamine-like effects and increased locomotor activity.

### 12.1 Mechanism of Action

The mechanism of action of bupropion is unknown, as is the case with other antidepressants. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monooxygenase oxidation or the re-uptake of serotonin.

### 12.3 Pharmacokinetics

Bupropion is a racemic mixture. The pharmacokinetic activity and pharmacokinetics of the individual enantiomers have not been studied.

Following chronic dosing of APLENZIN 348 mg once-daily tablets, the mean peak steady-state plasma concentration and area under the curve of bupropion were 134.3 (±38.5) ng/mL and 1409 (±346) ng·h/mL, respectively. Steady-state plasma concentrations of bupropion were reached within 8 days. The elimination half-life (±SD) of bupropion after a single dose is 21.3 (±6.7) hours.

In a study comparing 10-day dosing with APLENZIN 348 mg once-daily and bupropion HCl extended-release 300 mg once-daily (following a 3-day titration with bupropion HCl extended-release 150 mg once-daily), APLENZIN peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion) were equivalent to bupropion HCl extended-release 300 mg, with the average being 8.14% lower.

In a single dose study, two APLENZIN tablets 174 mg once-daily and one APLENZIN tablet 348 mg once-daily were evaluated. Equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

A multiple-dose study compared 14-day dosing with APLENZIN tablets 348 mg once-daily to dosing with three APLENZIN tablets 174 mg once-daily, following a 3-day titration with one APLENZIN tablet 174 mg once-daily, and a succeeding 5-day titration with two APLENZIN tablets 174 mg once-daily. Equivalence was demonstrated for peak plasma concentration and area under the curve for bupropion and the 3 metabolites.

These findings demonstrate that APLENZIN tablets 174 mg, 348 mg, and 522 mg are dose proportional.

### Absorption

Following single oral administration of APLENZIN tablets to healthy volunteers, the median time to peak plasma concentrations for bupropion was approximately 5 hours. The presence of food did not affect the peak concentration and time to peak plasma concentration of bupropion; the area under the curve was increased by 19%.

### Distribution

In vitro tests demonstrated that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that of 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 threo- and erythrohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of methoxybupropion, which is then excreted in the urine as the glucuronide metabolite. The polarity 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 threo- and erythrohydrobupropion are 5- to 10-fold less potent than bupropion. This may be of clinical importance, because the plasma concentrations of the metabolites are as high or higher than those of bupropion. Following chronic administration in healthy volunteers, peak plasma concentration of hydroxybupropion occurred approximately 6 hours after administration of APLENZIN. The peak plasma concentrations of threo- and erythrohydrobupropion were approximately 3 times the peak plasma concentration of threo- and erythrohydrobupropion at steady state. The elimination half-life of hydroxybupropion is approximately 24.3-49.9 hours, and its AUC at steady state is about 15.6 times that of bupropion. The times to peak concentrations for the threo- and erythrohydrobupropion metabolites are similar to that of hydroxybupropion. However, the elimination...
half-lives of erythroxylbupropion and threohydrobupropion are longer, approximately 31.1 (±7.6) and 50.8 (±8.5) hours, respectively, and steady-state AUCs were 1.5 and 6.8 times that of bupropion, respectively. Bupropion and its metabolites exhibit linear kinetics following chronic administration of 300 mg to 450 mg/day of bupropion hydrochloride (equivalent to 348 mg and 522 mg of APLENZIN, respectively). 

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/Smokers

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 can be affected by reduced 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-study comparison between normal subjects and patients 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 2.5- and 2.6-fold increase, respectively, in AUC for patients with end-stage renal failure. A second study, comparing normal subjects and patients with moderate-to-severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that after a single 150 mg dose administration of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in patients with impaired renal function, while levels of the hydroxylbupropion and threohydrobupropion 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. APLENZIN should be used with caution in patients with renal impairment.

Hepatic impairment

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study demonstrated that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be higher (by 33% to 87%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal. The second study demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, Cmax and Tmax) and its active metabolites (t1/2) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion Cmax and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs. 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean Cmax was approximately 66% lower. For the combined single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that in younger subjects. These data suggest that there is no prominent effect of age on the pharmacokinetics of bupropion.

Potential for APLENZIN to Affect Other Drugs

Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In a study of healthy volunteers, following a 14-day administration of bupropion 300 mg per day to 8 healthy male volunteers, there was no evidence of induction of its own metabolism. Nevertheless, there may be potential for clinical and/or inadvertent alterations of blood levels of coadministered drugs.

Drugs Metabolized by CYBP26

In vitro, bupropion and hydroxybupropion are CYP26P2 inhibitors. In a clinical study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of CYBP26P2, bupropion 300 mg per day followed by a single dose of 50 mg desipramine increased the Cmax and AUC of desipramine by approximately 66% and 67%, respectively. The effect was detectable from the first dose and persisted for 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYBP26P2 has not been formally studied.

Citalopram: Although citalopram is not primarily metabolized by CYBP26P2, in one study 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 NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifelong carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day of bupropion hydrochloride, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/kg basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day of bupropion hydrochloride. The maximum tolerated dose (MTD) could not be established in this study.

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 observed. Bupropion was produced in a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in one Ames bacterial mutagenicity assay, but was negative in another. 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/kg/day revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

14.1 Major Depressive Disorder

The efficacy of bupropion in the treatment of major depressive disorder was established with the immediate-release formulation of bupropion hydrochloride in two 4-week, placebo-controlled trials in adult inpatients with MDD and in one 6-week, parallel group trial in adult outpatients with MDD. In the first study, the bupropion dose range was 300 mg to 600 mg per day administered in 3 divided doses; 79% of patients were treated with doses of 300 mg to 450 per day. This trial demonstrated the efficacy of bupropion as measured by the Hamilton Depression Rating Scale (HDRS) total score, the HDRS item 1, and the Montgomery-Asberg Depression Rating Scale (MADRS) total score. In the second study included 2 fixed doses of bupropion (300 mg and 450 mg per day) and placebo. This trial demonstrated the efficacy of bupropion for only the 450-mg dose. The efficacy results were significant for the HDRS total score and the CGI-S severity score, but not for HDRS item 1. In the third 12 week, fixed-dose, double-blind, placebo-controlled trial with bupropion 300 mg per day. This study demonstrated the efficacy 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 (CG-I) score. A long-term, placebo-controlled, randomized withdrawal trial demonstrated the efficacy of bupropion HCl sustained-release in the maintenance treatment of MDD. The trial included adult outpatients meeting DSM-IV criteria for MDD, meeting criteria for performance of various treatment intervals of bupropion 300 mg per day. Responders were randomized to continue treatment of bupropion 300 mg or placebo, for up to 44 weeks of observation for relapse. Response during the open-label phase was defined as a CGI-Improvement Scale score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse was defined as a return to a score of 4 or 5 on the CGI-S following a previous 3-week interval of improvement or maintenance.

14.2 Impaired Cognition

In a placebo-controlled, double-blind, parallel group study, 61 patients with moderate to severe Alzheimer’s disease were randomized to receive bupropion 300 mg or placebo once daily for 12 weeks. The primary endpoint, a composite score of cognitive function as measured by the Alzheimer’s Disease Cooperative Study-11 (ADCS-11), was not statistically significant between treatment groups. However, the treatment groups did differ in measures of depression, with significantly lower Montgomery-Asberg Depression Rating Scale (MADRS) scores in the bupropion group compared to placebo. The authors suggested that this result may be related to the positive effect of bupropion on mood, which could affect cognition.

14.3 Nonsmokers

In a randomized, placebo-controlled trial, 197 nonsmokers with moderate to severe Alzheimer’s disease were randomized to receive bupropion 300 mg or placebo once daily for 12 weeks. The primary endpoint, a composite score of cognitive function as measured by the Alzheimer’s Disease Cooperative Study-11 (ADCS-11), was not statistically significant between treatment groups. However, the treatment groups did differ in measures of depression, with significantly lower Montgomery-Asberg Depression Rating Scale (MADRS) scores in the bupropion group compared to placebo. The authors suggested that this result may be related to the positive effect of bupropion on mood, which could affect cognition.

14.4 Eating Disorders

In a randomized, placebo-controlled trial, 197 nonsmokers with moderate to severe Alzheimer’s disease were randomized to receive bupropion 300 mg or placebo once daily for 12 weeks. The primary endpoint, a composite score of cognitive function as measured by the Alzheimer’s Disease Cooperative Study-11 (ADCS-11), was not statistically significant between treatment groups. However, the treatment groups did differ in measures of depression, with significantly lower Montgomery-Asberg Depression Rating Scale (MADRS) scores in the bupropion group compared to placebo. The authors suggested that this result may be related to the positive effect of bupropion on mood, which could affect cognition.

14.5 Sleep Disorder

In a randomized, placebo-controlled trial, 197 nonsmokers with moderate to severe Alzheimer’s disease were randomized to receive bupropion 300 mg or placebo once daily for 12 weeks. The primary endpoint, a composite score of cognitive function as measured by the Alzheimer’s Disease Cooperative Study-11 (ADCS-11), was not statistically significant between treatment groups. However, the treatment groups did differ in measures of depression, with significantly lower Montgomery-Asberg Depression Rating Scale (MADRS) scores in the bupropion group compared to placebo. The authors suggested that this result may be related to the positive effect of bupropion on mood, which could affect cognition.
Although there are no independent trials demonstrating the efficacy of APLENZIN or bupropion HCl extended-release in the acute treatment of MDD, studies have demonstrated similar bioavailability between the immediate-, sustained-, and extended-release formulations of bupropion HCl under steady-state conditions (i.e., the exposures [Cmax and AUC] for bupropion and its metabolites are similar among the 3 formulations). Furthermore, clinical studies have demonstrated that APLENZIN is bioequivalent to bupropion HCl extended-release.

14.2 Seasonal Affective Disorder

The efficacy of bupropion hydrochloride extended-release in the prevention of seasonal major depressive episodes associated with SAD was established in 3 randomized, double-blind, placebo-controlled trials with a history of seasonal depression (as defined by DSM-IV criteria). Bupropion treatment was initiated prior to the onset of symptoms in the autumn (September to November). Treatment was discontinued following a 2 week taper that began during the first week of spring (fourth week of March), resulting in a treatment duration of approximately 4 to 6 months for the majority of patients. Patients were randomized to treatment with bupropion HCl extended-release or placebo. The initial bupropion dose was 150 mg once daily for 1 week, followed by up-titration to 300 mg once daily. Patients who were deemed by the investigator to be unlikely or unable to tolerate 300 mg once daily were allowed to remain on, or had their dose reduced to, 150 mg once daily for the remainder of the study. Although, treatment differences in the 3 trials ranged from 267 mg to 280 mg per day. Approximately 59% of patients continued in the study for 3 to 6 months; 26% continued for <3 months, 15% continued for >6 months.

To enter the trials, patients must have had a low level of depressive symptoms, as demonstrated by a score of <7 on the Hamilton Depression Rating Scale-17 (HAM-D-17) and a HAMD-24 score of <14. The primary efficacy measure was the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders (SIGH-SAD), which is identical to the HAM-D-24. The SIGH-SAD consists of the HAMD-17 plus 7 items specifically assessing core symptoms of seasonal affective disorder; social withdrawal, weight gain, increased appetite, increased eating, carbohydrate craving, hypersomnia, and fatigability. The primary efficacy endpoint was the onset of a seasonal major depressive episode. The criteria for defining an episode included: 1) the investigator’s judgment that a major depressive episode had occurred or that the patient required intervention for depressive symptoms, or 2) a SIGH-SAD score of >23 on 2 consecutive weeks. The primary analysis was a comparison of depression-free rates between the bupropion and placebo groups.

In these 3 trials, the percentage of patients who were depression-free (did not have an episode of MDD) at the end of treatment was significantly higher in the bupropion group than in the placebo group: 81.4% vs. 69.7%, 87.0% v. 78.7%, and 84.0% vs. 69.0% for Trials 1, 2, and 3, respectively. For the 3 trials combined, the depression-free rate was 84.3% versus 72.6%, in the bupropion and placebo group, respectively.

14.3 Comparison to Other Antidepressants

In 1 study, the efficacy of extended-release APLENZIN (348 mg) was compared with that of 2 immediate-release bupropion products. Patients randomized to treatment with bupropion HCl extended-release or placebo. The initial bupropion dose was 150 mg once daily for 1 week, followed by up-titration to 300 mg once daily. Patients who were deemed by the investigator to be unlikely or unable to tolerate 300 mg once daily were allowed to remain on, or had their dose reduced to, 150 mg once daily for the remainder of the study. Although, treatment differences in the 3 trials ranged from 267 mg to 280 mg per day. Approximately 59% of patients continued in the study for 3 to 6 months; 26% continued for <3 months, 15% continued for >6 months.

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In these 3 trials, the percentage of patients who were depression-free (did not have an episode of MDD) at the end of treatment was significantly higher in the bupropion group than in the placebo group: 81.4% vs. 69.7%, 87.0% v. 78.7%, and 84.0% vs. 69.0% for Trials 1, 2, and 3, respectively. For the 3 trials combined, the depression-free rate was 84.3% versus 72.6%, in the bupropion and placebo group, respectively.

14.4 Potential for Developmental and Fetal Toxicity

There are no adequate and well-controlled studies in pregnant women. Bupropion should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When administered to pregnant rats and rabbits, bupropion increased the number of stillborns and decreased the number of live births. There were no differences in birth weight or mortality. Bupropion did not produce harmful effects to the developing fetus in rats and rabbits when administered during the period of organogenesis.

14.5 Congenital Anomalies

There have been reports of congenital anomalies among infants whose mothers took bupropion during pregnancy. The incidence of these anomalies in exposed infants cannot be reliably estimated from available data. Because animal reproduction studies are not always predictive of human response, and because bupropion is known to cross the placenta, bupropion should be given to pregnant women only if the potential benefit justifies the potential risk to the fetus.

14.6 Lactation

Although there are no independent trials demonstrating the efficacy of APLENZIN or bupropion HCl extended-release in the acute treatment of MDD, studies have demonstrated similar bioavailability between the immediate-, sustained-, and extended-release formulations of bupropion HCl under steady-state conditions (i.e., the exposures [Cmax and AUC] for bupropion and its metabolites are similar among the 3 formulations). Furthermore, clinical studies have demonstrated that APLENZIN is bioequivalent to bupropion HCl extended-release.

14.7 Pharmacokinetics

The primary site of action of APLENZIN is the brain, where it is known to have a high affinity for norepinephrine (NE) and dopamine (DA) transporter sites, with lower affinity for serotonin (5HT) transporter sites. The primary metabolite of bupropion is levodopa, which is converted to dopamine by aromatic L-amino acid decarboxylase. Bupropion has a plasma half-life of 12 to 24 hours, with a mean steady-state volume of distribution of approximately 150 L. Approximately 50% of bupropion is excreted unchanged in the urine and 30% is excreted as metabolites. The plasma clearance of bupropion is approximately 100 mL/min. The primary route of elimination of bupropion is by hepatic metabolism.

15.1 Interactions

Potentially drug interacting agents include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors (SNRIs), other anorectics, and certain anxiolytics. When bupropion is administered concomitantly with other medications that use the same CYP enzymes, drug interactions may occur. Therefore, with the exception of leucine deplete, avoid concomitant use of bupropion with other medications that use the same CYP enzymes, drug interactions may occur. Therefore, with the exception of leucine deplete, avoid concomitant use of bupropion with other medications that use the same CYP enzymes, drug interactions may occur. Therefore, with the exception of leucine deplete, avoid concomitant use of bupropion with other medications that use the same CYP enzymes, drug interactions may occur. Therefore, with the exception of leucine deplete, avoid concomitant use of bupropion with other medications that use the same CYP enzymes, drug interactions may occur. Therefore, with the exception of leucine deplete, avoid concomitant use of bupropion with other medications that use the same CYP enzymes, drug interactions may occur.
Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

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

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

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

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

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

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

Although APLENZIN is not a treatment for quitting smoking, it contains a form of the same active ingredient (bupropion hydrobromide) as ZYBAN® which is used to help people quit smoking. Some people have had changes in behavior, hostility, agitation, depression, suicidal thoughts or actions while taking bupropion to help them quit smoking. These symptoms can develop during treatment with bupropion or after stopping treatment with bupropion.

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

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

When you try to quit smoking, with or without bupropion, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression. Before taking bupropion, tell your healthcare provider if you have ever had depression or other mental illnesses. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without bupropion.

What Other Important Information Should I Know About APLENZIN?

- Seizures: There is a chance of having a seizure (convulsion, fit) with APLENZIN, especially in people:
  - with certain medical problems
  - who take certain medicines

The chance of having seizures increases with higher doses of APLENZIN. For more information, see the sections “Who should not take APLENZIN?” and “What should I tell my healthcare provider before using APLENZIN?” Tell your healthcare provider about all of your medical conditions and all the medicines you take. Do not take any other medicines while you are using APLENZIN unless your healthcare provider has said it is okay to take them. If you have a seizure while taking APLENZIN, stop taking the tablets and call your healthcare provider right away. Do not take APLENZIN again if you have a seizure.

- High blood pressure (hypertension): Some people get high blood pressure, that can be severe, while taking APLENZIN. The chance of high blood pressure may be higher if you also use nicotine replacement therapy (such as a nicotine patch) to help you stop smoking.

- Severe allergic reactions: Some people have severe allergic reactions to APLENZIN. Stop taking APLENZIN and call your healthcare provider right away if you get a rash, itching, hives, fever, swollen lymph glands, painful sores in the mouth or around the eyes, swelling of the lips or tongue, chest pain, or trouble breathing. These could be signs of a serious allergic reaction.

- Unusual thoughts or behaviors: Some people may have unusual thoughts or behaviors while taking APLENZIN, including delusions (believe you are someone else), hallucinations (seeing or hearing things that are not there), paranoia (feeling that people are against you), or feeling confused. If this happens to you, call your healthcare provider.

Visual Problems

- eye pain
- changes in vision
- swelling or redness in or around the eye

Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.

Manic episodes: Some people may have periods of mania while taking APLENZIN, including:

- greatly increased energy
- severe trouble sleeping
- racing thoughts
- reckless behavior
- unusually grand ideas
- excessive happiness or irritability
- talking more or faster than usual

If you have any of the above symptoms of mania, call your healthcare provider.
What is APLENZIN?
APLENZIN is a prescription medicine used to treat people with a certain type of depression called major depressive disorder and for the prevention of autumn-winter seasonal depression (seasonal affective disorder).

Who should not take APLENZIN?

Do not take APLENZIN if you:
- have or had a seizure disorder or epilepsy
- have or had an eating disorder such as anorexia nervosa or bulimia
- drink a lot of alcohol and abruptly stop drinking, or use medicines called sedatives (these make you sleepy) or benzodiazepines and you stop using them all of a sudden
- have within the last 14 days medicine called a monoamine oxidase inhibitor (MAOI), such as NARDIL™ (phenelzine sulfate), PARNATE™ (tranylcypromine sulfate), or MARPLAN® (isocarboxazid)
- are allergic to the active ingredient in APLENZIN, bupropion hydrobromide, or to any of the inactive ingredients. See the end of this leaflet for a complete list of ingredients in APLENZIN.

What should I tell my healthcare provider before using APLENZIN?
Tell your healthcare provider if you have ever had depression, suicidal thoughts or actions, or other mental health problems. See “Antidepressant Medicines, Depression, and Other Mental Illnesses, and Suicidal Thoughts or Actions.”

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Many medicines increase your chances of having seizures or cause other serious side effects if you take them while you are using APLENZIN.

If you take APLENZIN, you should not take any other medicines that contain bupropion including:
- ZYBAN®, WELLBUTRIN® Tablets
- WELLBUTRIN® SR Sustained-Release Tablets
- WELLBUTRIN XL® Extended-Release Tablets.

Bupropion is the same active ingredient that is in APLENZIN.

How should I take APLENZIN?

Take APLENZIN exactly as prescribed by your healthcare provider.

Do not chew, cut, or crush APLENZIN tablets. If you do the medicine will be released into your body too quickly. If this happens you may be more likely to get side effects including seizures. You must swallow the tablets whole. Tell your healthcare provider if you cannot swallow medicine tablets.

Take APLENZIN in the morning.

You may take APLENZIN with or without food.

If you miss a dose, do not take an extra tablet to make up for the dose you forgot. Wait and take your next tablet at the regular time.

This is very important. Too much APLENZIN can increase your chance of having a seizure.

If you take too much APLENZIN, or overdose, call your local emergency room or poison control center right away.

The APLENZIN tablet is covered by a shell that slowly releases the medicine inside your body. You may notice something in your stool that looks like a tablet. This is normal. This is the empty shell passing from your body.

Do not take any other medicines while using APLENZIN unless your healthcare provider has told you it is okay.

If you are taking APLENZIN for the treatment of major depressive disorder, it may take several weeks for you to feel that APLENZIN is working. Once you feel better, it is important to keep taking APLENZIN exactly as directed by your healthcare provider. Call your healthcare provider if you do not feel APLENZIN is working for you.

If you are taking APLENZIN for the prevention of seasonal major depressive episodes associated with seasonal affective disorder, it is important to keep taking APLENZIN through the autumn-winter season, or as directed by your healthcare provider.

Do not change your dose or stop taking APLENZIN without first talking with your healthcare provider first.

What should I avoid while taking APLENZIN?

Do not drink alcohol while using APLENZIN. If you usually drink a lot of alcohol, talk with your healthcare provider before suddenly stopping. If you suddenly stop drinking alcohol, you may increase your chance of having seizures.

Do not drive a car or use heavy machinery until you know how APLENZIN affects you. APLENZIN can impair your ability to perform these tasks.

What are the possible side effects of APLENZIN?

See “What is the most important information I should know about APLENZIN?”

APLENZIN may cause serious side effects, including:

The most common side effects of APLENZIN include:
- dry mouth
- nausea
- trouble sleeping
- dizziness
- sore throat
- stomach pain
- agitation
- anxiety
- shakiness
- fast heartbeat
- sweating
- ringing in the ears
- muscle pain
- anorexia
- urinating more than normal for you
- rash

Tell your healthcare provider right away about any side effects that bother you.

These are not all the possible side effects of APLENZIN. For more information, ask your healthcare provider or pharmacist.

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

You may also report side effects to Valeant Pharmaceuticals North America LLC at 1-877-361-2719.

How should I store APLENZIN?

Store APLENZIN at room temperature between 59°F and 86°F (15°C to 30°C).

Keep APLENZIN and all medicines out of the reach of children.

General information about APLENZIN

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use APLENZIN for a condition for which it was not prescribed. Do not give APLENZIN to other people, even if they have the same symptoms you have. It may harm them.
- If you take a urine drug screening test, APLENZIN may make the test result positive for amphetamines. If you tell the person giving you the drug screening test that you are taking APLENZIN, they can do a more specific drug screening test that should not have this problem.

This Medication Guide summarizes the most important information about APLENZIN. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about APLENZIN that is written for healthcare professionals.

For more information about APLENZIN, go to www.APLENZIN.com or call 1-800-633-1610.
What are the ingredients in APLENZIN?
Active ingredient: bupropion hydrobromide
Inactive ingredients: ethylcellulose, glyceryl behenate, polyvinyl alcohol, polyethylene glycol, povidone, and dibutyl sebacate. Carnauba wax is included in the 174 mg and 348 mg strengths. The tablets are printed with edible black ink.
The following are registered trademarks of their respective manufacturers: WELLBUTRIN®/GlaxoSmithKline; WELLBUTRIN XL®/GlaxoSmithKline; ZYBAN®/GlaxoSmithKline

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Rx only

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