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) Tablet, Film Coated, Extended-Release for Oral use
Initial U.S. Approval: 1985

----------RECENT MAJOR CHANGES----------

Boxed Warning	**09/2009**
Warnings and Precautions (5.2)	**09/2009**
Patient Counseling Information	**09/2009**

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS
See full prescribing information for complete boxed warning.

Use in Treating Psychiatric Disorders

- **Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. (5.1, 8.4)**
- **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. (8.4)**
- **Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. (5.1)**
- **Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. (5.1)**
- **Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. (5.1)**
- **Families and caregivers should be advised of the need for close observation and communication with the prescriber. (17)**
- **Aplenzin is not approved for use in pediatric patients. [See *WARNINGS AND PRECAUTIONS* , Clinical Worsening and Suicide Risk (5.1) and *USE IN SPECIFIC POPULATIONS* , Pediatric Use (8.4)]**

Use in Smoking Cessation Treatment

- **Aplenzin is not approved for smoking cessation treatment, but bupropion under the name of ZYBAN® is approved for this use. (5.2)**
- **Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. (BOXED WARNING, 5.2)**

----------INDICATIONS AND USAGE----------
Aplenzin is an aminoketone antidepressant, indicated for the treatment of Major depressive disorder. (1)
Periodically reevaluate long-term usefulness for the individual patient. (1)

----------DOSAGE AND ADMINISTRATION----------
General: Increase dose gradually to reduce seizure risk and other effects. (2.1)
Recommendations for Adults:

- Start: 174 mg/day. Usual target: 348 mg/day. (2.2)
  Periodically reassess dose and need for maintenance treatment. (2.3)
- Switching from Wellbutrin®, Wellbutrin® SR, Wellbutrin XL® (2.4)
  Patients should be given equivalent daily doses, if possible.
- Impaired Hepatic Function, Impaired Renal Function (2.5, 2.6) Reduce dose and/ or frequency. Severe cirrhosis: max. 174 mg/48 hours.

----------DOSAGE FORMS AND STRENGTHS---------

- 174 mg Aplenzin extended-release tablets (3)
- 348 mg Aplenzin extended-release tablets (3)
- 522 mg Aplenzin extended-release tablets (3)

----------CONTRAINDICATIONS----------

- Patients with seizure disorder (4)
- Patients using other bupropion products, including Zyban® (4)
- Current or prior diagnosis of bulimia or anorexia nervosa (4)
- Abrupt discontinuation of alcohol, sedatives (incl. benzodiazepines) (4)
- Use of MAO inhibitor; stop at least 2 weeks prior to bupropion use (4)
- Patients allergic to any of the ingredients of Aplenzin (4)

----------WARNINGS AND PRECAUTIONS-----

- Suicide risk: Closely monitor high risk patients and all other patients (BOXED WARNING, 5.1, 5.2, 8.4)
- Serious neuropsychiatric symptoms and suicide risk have been reported in patients taking bupropion for smoking cessation; symptoms of nicotine withdrawal complicate these issues. Aplenzin is not approved for smoking cessation. (5.2)
- Risk of activation of psychosis and/or mixed/manic episodes (5. 3)
  Screen patients for bipolar disorder. Aplenzin is not approved for bipolar depression. (5.4)
- Seizure risk: Can be minimized by limiting daily dose to 522 mg and slow dose increase. Extreme caution with high risk patients (5.5 , 4, 7.4)
- Hepatic impairment: Use with caution; reduce dose and/or frequency. Severe hepatic cirrhosis: Extreme caution; max. 174 mg/48 hours (5.6)
- Potential for hepatotoxicity (5.7)
- Risk of restlessness, agitation, anxiety, insomnia (5.8) ; risk of neuropsychiatric events, incl. delusions, hallucinations, psychosis, concentration disturbance, paranoia, confusion (5.9)
- Loss of appetite should be considered if weight loss is a concern (5.10)
- Risk of anaphylactic/oid reactions; erythema multiforme, Stevens-Johnson syndrome; risk of arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity (5.11)
- Risk of severe hypertension; may require acute treatment. Caution in patients with recent history of MI or unstable heart disease (5.12)

----------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 substrates or inhibitors (e.g. cyclophosphamide, orphenadrine, thiotepa, ticlopidine, and clopidogrel), efavirenz, fluvoxamine, norfluoxetine, nelfinavir, paroxetine, ritonavir, sertraline: May increase bupropion activity (7)
- Carbamazepine, phenobarbital, phenytoin: May induce bupropion metabolism (7)
- Bupropion may be an inducer of drug metabolizing enzymes (7)
- Drugs metabolized by CYP2D6, e.g. certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide): Consider dose reduction when using with bupropion. Bupropion & hydroxybupropion inhibit CYP2D6 (7.1)
- MAO inhibitors: Increase bupropion toxicity. Contraindicated (4, 7.2)
- Levodopa, amantadine: Cautious bupropion dosing (7.3)
- Drugs that lower seizure threshold: Cautious bupropion dosing (5.5, 7.4)
- Nicotine transdermal system: Monitor for severe hypertension (5.12)
- Alcohol: Minimize consumption or avoid (7.6)
- Drug laboratory test interactions: Bupropion therapy may cause false-positive urine immunoassay screening test results for amphetamines (7.7).

----------USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Use only if benefit outweighs potential risk to the fetus (8.1)
- Nursing: Breast feeding or drug should be discontinued (8.3)
- Children: Safety & effectiveness not established. Balance risk/need (8.4)
- Renal Impairment: Reduce dose and/or frequency (8.6)
- Hepatic impairment: Use with caution; reduce dose and/or frequency. Severe cirrhosis: Extreme caution; max. 174 mg/48 hours (8.7)

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

Revised: [06/2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

Aplenzin® (bupropion hydrobromide) Extended-Release Tablets

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Use in treating Psychiatric Disorders: Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of 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 in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. **Families and caregivers should be advised of the need for close observation and communication with the prescriber. Aplenzin is not approved for use in pediatric patients [See *WARNINGS AND PRECAUTIONS,* Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders *(5.1)* and *USE IN SPECIFIC POPULATIONS, Pediatric Use (8.4)*].**

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

All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the post-marketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with

and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of ZYBAN.

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

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as six months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial ***[See WARNINGS AND PRECAUTIONS: Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment (5.2) and PATIENT COUNSELING INFORMATION (17)]***

1 INDICATIONS AND USAGE

Aplenzin® (bupropion hydrobromide extended-release tablets) is indicated for the treatment of major depressive disorder.

The efficacy of bupropion in the treatment of a major depressive episode was established in two 4-week controlled trials of inpatients and in one 6-week controlled trial of outpatients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) [see ***CLINICAL STUDIES (14)***].

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

The efficacy of bupropion in maintaining an antidepressant response for up to 44 weeks following 8 weeks of acute treatment was demonstrated in a placebo-controlled trial with the sustained-release formulation of bupropion [see ***CLINICAL STUDIES (14)***]. Nevertheless, the physician who elects to use Aplenzin for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Considerations

It is particularly important to administer Aplenzin Tablets in a manner most likely to minimize the risk of seizure [**see** ***WARNINGS AND PRECAUTIONS: Seizures (5.5)***]. Gradual escalation in dosage is also important if agitation, motor restlessness, and insomnia, often seen during the initial days of treatment, are to be minimized. If necessary, these effects may be managed by temporary reduction of dose or the short-term administration of an intermediate to long-acting sedative hypnotic. A sedative hypnotic usually is not required beyond the first week of treatment. Insomnia may also be minimized by avoiding bedtime doses. If distressing, untoward effects supervene, dose escalation should be stopped. Aplenzin should be swallowed whole and not crushed, divided, or chewed. Aplenzin may be taken without regard to meals.

2.2 Initial Treatment

The usual adult target dose for Aplenzin Tablets is 348 mg/day (equivalent to 300 mg/day bupropion HCl), given once daily in the morning. Dosing with Aplenzin Tablets should begin at 174 mg/day (equivalent to 150 mg/day bupropion HCl) given as a single daily dose in the morning. If the 174 mg initial dose is adequately tolerated, an increase to the 348 mg/day target dose, given as once daily, may be made as early as day 4 of dosing. There should be an interval of at least 24 hours between successive doses.

Increasing the Dosage Above 348 mg/day: As with other antidepressants, the full antidepressant effect of Aplenzin Tablets may not be evident until 4 weeks of treatment or longer. An increase in dosage to the maximum of 522 mg/day, given as a single dose, may be considered for patients in whom no clinical improvement is noted after several weeks of treatment at 348 mg/day.

2.3 Maintenance Treatment

It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacological therapy beyond response to the acute episode. It is unknown whether or not the dose of Aplenzin needed for maintenance treatment is identical to the dose needed to achieve an initial response. Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment.

2.4 Switching Patients from WELLBUTRIN, WELLBUTRIN SR or WELLBUTRIN XL

When switching patients from WELLBUTRIN®, WELLBUTRIN® SR or WELLBUTRIN XL® Tablets to Aplenzin, give the equivalent total daily dose when possible (522 mg bupropion HBr are equivalent to 450 mg bupropion HCl; 348 mg bupropion HBr are equivalent to 300 mg bupropion HCl; 174 mg bupropion HBr are equivalent to 150 mg bupropion HCl). Patients who are currently being treated with WELLBUTRIN Tablets at 300 mg/day (for example, 100 mg 3 times a day) may be switched to Aplenzin 348 mg once daily. Patients who are currently being

treated with WELLBUTRIN SR Sustained-Release Tablets at 300 mg/day (for example, 150 mg twice daily) may be switched to Aplenzin 348 mg once daily.

2.5 Dosage Adjustment for Patients with Impaired Hepatic Function

Aplenzin should be used with extreme caution in patients with severe hepatic cirrhosis. The dose should not exceed 174 mg every other day in these patients. Aplenzin should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and a reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis [see ***WARNINGS AND PRECAUTIONS: Hepatic Impairment (5.6)***, ***USE IN SPECIFIC POPULATION: Hepatic Impairment (8.7)***, and ***CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3)***].

2.6 Dosage Adjustment for Patients with Impaired Renal Function

Aplenzin 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: Renal Impairment (8.6)*** and ***CLINICAL PHARMACOLOGY, Pharmacokinetics (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” in bottles of 30 tablets.

Aplenzin Extended-Release Tablets, 348 mg of bupropion hydrobromide, are white to off white, round tablets printed with “BR” over “348” in bottles of 30 tablets .

Aplenzin Extended-Release Tablets, 522 mg of bupropion hydrobromide, are white to off white, round tablets printed with “BR” over “522” in bottles of 30 tablets .

4 CONTRAINDICATIONS

Aplenzin is contraindicated in patients with a seizure disorder.

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

Aplenzin is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.

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

The concurrent administration of Aplenzin Tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with Aplenzin Tablets.

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

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 suicidality 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 beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

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

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

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases [see *BOXED WARNING* and *USE IN SPECIFIC POPULATIONS: Pediatric Use (8.4)*].

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

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

Families and caregivers of patients being treated with antidepressants for major depressive disorder 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 health care providers. Such monitoring

should include daily observation by families and caregivers.*[See also PATIENT COUNSELING INFORMATION (17)]* Prescriptions for Aplenzin should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

APLENZIN is not approved for smoking cessation treatment, but bupropion under the name ZYBAN is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation [see ***BOXED WARNING*** and ***ADVERSE REACTIONS (6)***]**. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.** Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke. When symptoms were reported, most were during bupropion treatment but some were following discontinuation of bupropion therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. All patients being treated with bupropion as part of smoking cessation treatment should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness.

Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of ZYBAN.

Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, 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 post-marketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, and some persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as six months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

5.3 Activation of Psychosis and/or Mania

Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. Aplenzin is expected to pose similar risks.

5.4 Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Aplenzin is not approved for use in treating bipolar depression.

Patients should be made aware that Aplenzin contains bupropion, the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that Aplenzin should not be used in combination with ZYBAN, or any other medications that contain bupropion, such as WELLBUTRIN XL (bupropion hydrochloride extended-release formulation), WELLBUTRIN SR (bupropion hydrochloride sustained-release formulation), or WELLBUTRIN (bupropion hydrochloride immediate-release formulation). [See also *PATIENT COUNSELING INFORMATION (17)*].

5.5 Seizures

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

The seizure incidence with Aplenzin has not been formally evaluated in clinical trials. Studies in mice suggest the potential for a significant reduction in the risk of seizure with bupropion HBr as compared to bupropion HCl. The seizure incidence is not expected to be worse than presented below for comparable doses of the immediate-release and sustained-release formulations of bupropion HCl.

- ***Dose***

At doses up to 300 mg/day (equivalent to 348 mg/day of bupropion HBr) of the sustained-release formulation of bupropion hydrochloride (WELLBUTRIN SR), the incidence of seizure is approximately 0.1% (1/1,000).

Data for the immediate-release formulation of bupropion hydrochloride revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day (equivalent to a range of 348 to 522 mg/day of bupropion HBr). This seizure incidence (0.4%) may exceed that of some other marketed antidepressants.

Additional data accumulated for the immediate-release formulation of bupropion hydrochloride suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day (equivalent to 522 and 696 mg/day bupropion HBr). The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of WELLBUTRIN XL (equivalent to 522 mg Aplenzin) Tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

- ***Patient Factors***

Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

- ***Clinical Situations***

Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin.

- ***Concomitant Medications***

Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold.

Recommendations for Reducing the Risk of Seizure:

Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if
- **the total daily dose of Aplenzin Tablets does *not* exceed 522 mg,**
- **the rate of incrementation of dose is gradual.**

Aplenzin should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold.

5.6 Hepatic Impairment

Aplenzin should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 174 mg every other day in these patients.

Aplenzin should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels.

See *DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Hepatic Function (2.5)*, *USE IN SPECIFIC POPULATIONS: Hepatic Impairment (8.7),* and ***CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3)*.**

5.7 Potential for Hepatotoxicity

In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted.

5.8 Agitation and Insomnia

Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion.
Patients in placebo-controlled trials of major depressive disorder with WELLBUTRIN SR, the sustained-release formulation of bupropion hydrochloride, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of WELLBUTRIN SR (Bupropion HCl Sustained-release Tablets) for Major Depressive Disorder

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

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

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

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

5.9 Psychosis, Confusion, and Other Neuropsychiatric Phenomena

Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment.

5.10 Altered Appetite and Weight

In placebo-controlled studies of major depressive disorder using WELLBUTRIN SR®, the sustained-release formulation of bupropion hydrochloride, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of WELLBUTRIN® SR (Bupropion Hydrochloride Sustained-release Tablets) for Major Depressive Disorder

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

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

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

5.11 Allergic Reactions

Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking Aplenzin and consult a doctor if experiencing allergic or

anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness.

5.12 Cardiovascular Effects

In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These reactions have been observed in both patients with and without evidence of preexisting hypertension.

Data from a comparative study of the sustained-release formulation of bupropion hydrochloride (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion hydrochloride 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 hydrochloride and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion hydrochloride and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion hydrochloride, NTS, and placebo, respectively. The majority of these patients had evidence of preexisting hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

There is no clinical experience establishing the safety of Aplenzin Tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups.

Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension.

5.13 Laboratory Tests

There are no specific laboratory tests recommended.

6 ADVERSE REACTIONS

The following risks are discussed in greater detail in other sections of the labeling:

- Clinical worsening and suicide risk [see ***WARNINGS AND PRECAUTIONS Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders (5.1)***]
- Activation of Psychosis and/or Mania [see ***WARNINGS AND PRECAUTIONS: Activation of Psychosis and/or Mania (5.3) and WARNINGS AND PRECAUTIONS: Screening Patients for Bipolar Disorder (5.4)***]
- Hepatotoxicity [see ***WARNINGS AND PRECAUTIONS: Potential for Hepatotoxicity(5.7)***]
- Agitation and Insomnia [see ***WARNINGS AND PRECAUTIONS: Agitation and Insomnia (5.8)***]
- Psychosis, confusion and other neuropsychiatric phenomena [see ***WARNINGS AND PRECAUTIONS: Psychosis, Confusion, and Other Neuropsychiatric Phenomena (5.9)***]
- Altered appetite [see ***WARNINGS AND PRECAUTIONS: Altered Appetite and Weight (5.10)***]
- Allergic reactions, including anaphylactoid/anaphylactic reactions, erythema multiforme, Stevens-Johnson syndrome and other symptoms suggestive of delayed hypersensitivity [see ***WARNINGS AND PRECAUTIONS: Allergic Reactions (5.11)***]
- Hypertension [see ***WARNINGS AND PRECAUTIONS: Cardiovascular Effects (5.12)***]

6.1 Commonly Observed Adverse Reactions in Controlled Clinical Trials

Adverse reactions from Table 5 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion hydrochloride and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups.

*300 mg/day of WELLBUTRIN SR (*equivalent *to 348 mg/day bupropion HBr)*: Anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

*400 mg/day of WELLBUTRIN SR (*equivalent *to 464 mg/day bupropion HBr)*: Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

Aplenzin is bioequivalent to WELLBUTRIN XL, which has been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion. The information included under this subsection and under the subsections 6.2 and 6.3 is based primarily on data from controlled clinical trials with WELLBUTRIN SR Tablets, the sustained-release formulation of bupropion hydrochloride.

6.2 Adverse Reactions Leading to Discontinuation of Treatment With WELLBUTRIN WELLBUTRIN SR

In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion hydrochloride and 4% of patients treated with placebo discontinued treatment due to adverse reactions. The specific adverse reactions in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of bupropion hydrochloride, and at a rate at least twice the placebo rate are listed in Table 4.

Table 4. Treatment Discontinuations Due to Adverse Reactions in Placebo-Controlled Trials for Major Depressive Disorder

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

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

In clinical trials with the immediate-release formulation of bupropion, 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 of bupropion hydrochloride, include vomiting, seizures, and sleep disturbances.

6.3 Adverse Reactions Occurring at an Incidence of 1% or More Among Patients Treated With WELLBUTRIN or WELLBUTRIN SR

Table 5 enumerates treatment-emergent adverse reactions that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion hydrochloride and with placebo in controlled trials. Reactions that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse reactions were classified using a COSTART-based Dictionary.

Accurate estimates of the incidence of adverse reactions associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward reactions in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions.

Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the reactions. A better perspective on the serious adverse reactions associated with the use of bupropion is provided in ***WARNINGS AND PRECAUTIONS section (5)*.**

Table 5. Treatment-Emergent Adverse Reactions in Placebo-Controlled Trials* for Major Depressive Disorder

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

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

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

Additional reactions to those listed in Table 5 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion hydrochloride (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%).

6.4 Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion

In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion hydrochloride in depressed patients and in nondepressed smokers, as well as in clinical trials and

postmarketing clinical experience with the immediate-release formulation of bupropion hydrochloride.

Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion hydrochloride. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion hydrochloride (n = 3,100). All treatment-emergent adverse events are included except those listed in Tables 2 through 5, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in ***WARNINGS AND PRECAUTIONS section (5).***

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with Aplenzin is unknown.

Body (General)
Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness [see ***WARNINGS AND PRECAUTIONS: Allergic Reactions (5.11)***].

Cardiovascular
Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe); [see ***WARNINGS AND PRECAUTIONS: Cardiovascular Effects (5.12)***], myocardial infarction, phlebitis, and pulmonary embolism.

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

Endocrine
Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.

Hemic and Lymphatic
Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin.

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

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

Nervous System
Frequent were agitation, depression, and irritability. Infrequent were abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory
Rare was bronchospasm. Also observed was pneumonia.

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

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

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

7 DRUG INTERACTIONS

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

Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. *In vitro* studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between Aplenzin and drugs that are substrates or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel). In addition, *in vitro* studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150 mg tablets of the sustained-release formulation of bupropion hydrochloride with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

In a series of studies in healthy volunteers, ritonavir (100mg twice daily or 600mg twice daily) or ritonavir 100mg plus lopinavir 400mg (KALETRA®) twice daily reduced exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20% to 80%. Similarly, efavirenz 600mg once daily for 2 weeks reduced the exposure of bupropion by approximately 55%. This effect of retonavir, KALETRA®, and efavirenz is thought to be due the induction of bupropion metabolism. Patients receiving any of these drugs with bupropion may need increased doses of bupropion, but the maximum recommended dose of bupropion should not be exceeded [see ***CLINICAL PHARMACOLOGY: Metabolism*** (*12.3*)].

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

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

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

7.1 Drugs Metabolized By Cytochrome P450IID6 (CYP2D6)

Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme *in vitro*. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion hydrochloride given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index.

Drugs which require metabolic activation by CYP2D6 in order to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion.

Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively. Citalopram did not affect the pharmacokinetics of bupropion and its 3 metabolites.

7.2 MAO Inhibitors

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

7.3 Levodopa and Amantadine

Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of Aplenzin Tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases.

7.4 Drugs That Lower Seizure Threshold

Concurrent administration of Aplenzin Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution [see ***WARNINGS AND PRECAUTIONS: Seizures (5.5)***]. Low initial dosing and gradual dose increases should be employed.

7.5 Nicotine Transdermal System

See ***WARNINGS AND PRECAUTIONS: Cardiovascular Effects (5.12)***].

7.6 Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with Aplenzin should be minimized or avoided [also see ***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

Teratogenic Effects

Pregnancy Category C**.** In studies conducted in rats and rabbits, bupropion hydrochloride was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater.

When rats were administered bupropion hydrochloride at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall, and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall, or cardiovascular malformations

specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. Aplenzin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of Aplenzin Tablets on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Aplenzin Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in the pediatric population have not been established [see ***BOXED WARNING*** and ***WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders (5.1)***]. Anyone considering the use of Aplenzin in a child or adolescent must balance the potential risks with the clinical need.

8.5 Geriatric Use

Of the approximately 6,000 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 and over 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, but greater sensitivity of some older individuals cannot be ruled out.

A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites [see ***CLINICAL PHARMACOLOGY, Pharmacokinetics (12.3)***].

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [**see** ***DOSAGE AND ADMINISTRATION: Dosage Adjustment in Patients With***

Impaired Renal Function (2.6), USE IN SPECIFIC POPULATIONS: Renal Impairment (8.6)].

8.6 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 C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. Aplenzin should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels [see ***DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Renal Function (2.6)*** and ***CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3)***].

8.7 Hepatic Impairment

Aplenzin should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 174 mg every other day in these patients.

Aplenzin should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis.

All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels [see ***DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Hepatic Function (2.5)*** and ***CLINICAL PHARMACOLOGY: Pharmacokinetics (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 hydrochloride (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement.

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

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

Animals

Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

10 OVERDOSAGE

10.1 Human Overdose Experience

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

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

10.2 Overdosage Management

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

Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

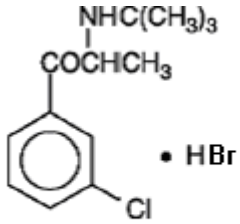
Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known.

Due to the dose-related risk of seizures with Aplenzin, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

11 DESCRIPTION

Aplenzin (bupropion hydrobromide), 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 (±)-2-(tert-butylamino)-3'-chloropropiophenone hydrobromide. The molecular weight is 320.6. The molecular formula is $C_{13}H_{18}ClNO•HBr$. Bupropion hydrobromide powder is white or almost white, crystalline, and soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



Aplenzin Tablets are supplied for oral administration as 174 mg, 348 mg, and 522 mg white to off white extended-release tablets. Each tablet contains the labeled amount of bupropion hydrobromide and the 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 insoluble shell of the extended-release tablet may remain intact during gastrointestinal transit and is eliminated in the feces.

12 CLINICAL PHARMACOLOGY

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.

12.2 Pharmacodynamics

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine, and does not inhibit monoamine oxidase or the re-uptake of serotonin.

12.3 Pharmacokinetics

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

Following chronic dosing of Aplenzin 348 mg Tablets, the mean peak steady-state plasma concentration and area under the curve of bupropion were 134.3 (± 38.2) ng/mL and 1409 (± 346) ng•hr/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 Tablets 348 mg once daily and WELLBUTRIN XL Tablets 300 mg once daily, following a 3-day titration with once daily WELLBUTRIN XL Tablets 150 mg, Aplenzin peak plasma concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, threohydrobupropion, and erythrohydrobupropion) were equivalent to WELLBUTRIN XL Tablets 300 mg, with the average being 8 to14% 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.

Additionally, a multiple dose study compared 14-day dosing with Aplenzin Tablets 522 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. A 348 mg dose can be achieved by administering either one Aplenzin Tablet 348 mg or two Aplenzin Tablets 174 mg. A 522 mg dose can be achieved by administering either one Aplenzin Tablet 522 mg, three Aplenzin Tablets 174 mg, or one Aplenzin Tablet 174 mg plus one Aplenzin Tablet 348 mg.

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; area under the curve was increased by 19%.

Distribution

In vitro tests show that bupropion is 84% bound to human plasma proteins at concentrations up to 200 mcg/mL. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion, whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Metabolism

Bupropion is extensively metabolized in humans. Three metabolites have been shown to be active: hydroxybupropion, which is formed via hydroxylation of the *tert*-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. *In vitro* findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. The potency and toxicity of the metabolites relative to bupropion have not been fully characterized. However, it has been demonstrated in an antidepressant screening test in mice that hydroxybupropion is one half as potent as bupropion, while threohydrobupropion and erythrohydrobupropion are 5-fold less potent than bupropion. This may be of clinical importance because the plasma concentrations of the metabolites are as high or higher than those of bupropion.

Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme, such as ritonavir or efavirenz. In a healthy volunteer study, ritonavir at a dose of 100mg twice daily reduced AUC and C_{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%.

In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the AUC and C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%.

In another healthy volunteer study, KALETRA® (lopinavir 400mg/ritonavir 100mg twice daily) decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of hydroxybupropion metabolite were decreased by by 50% and 2131%, respectively [see ***DRUG INTERACTIONS*** (***7***)].

In a study of healthy volunteers, efavirenz 600mg 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 C_{max} of hydroxybupropion was increased by 50%.

Although bupropion is not metabolized by cytochrome P450IID6 (CYP2D6), there is the potential for drug-drug interactions when bupropion is coadministered with drugs metabolized by this isoenzyme [see ***DRUG INTERACTIONS: Drugs Metabolized by Cytochrome P450IID6 (CYP2D6) (7.1)***].

Following chronic administration in healthy volunteers, peak plasma concentration of hydroxybupropion occurred approximately 6 hours after administration of Aplenzin tablets. The peak plasma concentrations of hydroxybupropion were approximately 9 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 24.3 (± 4.9) hours, and its AUC at steady state is about 15.6 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of hydroxybupropion. However, the elimination half-lives of erythrohydrobupropion and threohydrobupropion are longer, approximately 31.1(± 7.8) 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 to 450 mg/day of bupropion hydrochloride (equivalent to 348 mg and 522 mg of bupropion hydrobromide, respectively).

Elimination

Following oral administration of 200 mg of ^{14}C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. However, the fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion.

Population Subgroups

Factors or conditions altering metabolic capacity (e.g., liver disease, congestive heart failure [CHF], age, concomitant medications, etc.) or elimination may be expected to influence the degree and extent of accumulation of the active metabolites of bupropion. The elimination of the major metabolites of bupropion may be affected by reduced renal or hepatic function because they are moderately polar compounds and are likely to undergo further metabolism or conjugation in the liver prior to urinary excretion.

Hepatic

The effect of hepatic impairment on the pharmacokinetics of bupropion was characterized in 2 single-dose studies, one in patients with alcoholic liver disease and one in patients with mild to severe cirrhosis. The first study showed that the half-life of hydroxybupropion was significantly longer in 8 patients with alcoholic liver disease than in 8 healthy volunteers (32±14 hours versus 21±5 hours, respectively). Although not statistically significant, the AUCs for bupropion and hydroxybupropion were more variable and tended to be greater (by 53% to 57%) in patients with alcoholic liver disease. The differences in half-life for bupropion and the other metabolites in the 2 patient groups were minimal.

The second study showed no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 patients with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in patients with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in patients with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower. The mean AUC increased by about 1½-fold for hydroxybupropion and about 2½-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers [see ***DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Hepatic function (2.5)***, ***WARNINGS AND PRECAUTIONS: Hepatic Impairment (5.6),*** and ***USE IN SPECIFIC POPULATIONS: Hepatic Impairment (8.7)***].

Renal

There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An inter-study comparison between normal subjects and patients with endstage 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 2.3- and 2.8-fold increase, respectively, in AUC for patients with end-stage renal failure. The elimination of the major metabolites of bupropion may be reduced by impaired renal function [see ***DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Renal Function (2.6)*** and ***USE IN SPECIFIC POPULATIONS: Renal Impairment (8.6)***].

Left Ventricular Dysfunction

During a chronic dosing study with bupropion in 14 depressed patients with left ventricular dysfunction (history of CHF or an enlarged heart on x-ray), no apparent effect on the pharmacokinetics of bupropion or its metabolites was revealed, compared to healthy volunteers.

Age

The effects of age on the pharmacokinetics of bupropion and its metabolites have not been fully characterized, but an exploration of steady-state bupropion concentrations from several depression efficacy studies involving patients dosed in a range of 300 to 750 mg/day, on a 3 times daily schedule, revealed no relationship between age (18 to 83 years) and plasma concentration of bupropion. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects. These data suggest there is no prominent effect of age on bupropion concentration; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites [see ***USE IN SPECIFIC POPULATIONS: Geriatric Use (8.5)***].

Gender

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

Smokers

The effects of cigarette smoking on the pharmacokinetics of bupropion hydrochloride were studied in 34 healthy male and female volunteers; 17 were chronic cigarette smokers and 17 were nonsmokers. Following oral administration of a single 150-mg dose of bupropion, there was no statistically significant difference in C_{max}, half-life, T_{max}, AUC, or clearance of bupropion or its active metabolites between smokers and nonsmokers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day bupropion hydrochloride, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day of bupropion hydrochloride (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study.

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in 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

The efficacy of bupropion as a treatment for major depressive disorder was established with the immediate-release formulation of bupropion hydrochloride in two 4-week, placebo-controlled trials in adult inpatients and in one 6-week, placebo-controlled trial in adult outpatients. In the first study, patients were titrated in a bupropion hydrochloride dose range of 300 to 600 mg/day of the immediate-release formulation on a 3 times daily schedule; 78% of patients received maximum doses of 450 mg/day or less. This trial demonstrated the effectiveness of bupropion on the Hamilton Depression Rating Scale (HDRS) total score, the depressed mood item (item 1) from that scale, and the Clinical Global Impressions (CGI) severity score. A second study included 2 fixed doses of the immediate-release formulation of bupropion hydrochloride (300 and 450 mg/day) and placebo. This trial demonstrated the effectiveness of bupropion, but only at

the 450-mg/day dose of the immediate-release formulation; the results were positive for the HDRS total score and the CGI severity score, but not for HDRS item 1. In the third study, outpatients received 300 mg/day of the immediate-release formulation of bupropion hydrochloride. This study demonstrated the effectiveness of bupropion on the HDRS total score, HDRS item 1, the Montgomery-Asberg Depression Rating Scale, the CGI severity score, and the CGI improvement score.

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

Although there are no independent trials demonstrating the antidepressant effectiveness of Aplenzin or WELLBUTRIN XL, studies have demonstrated similar bioavailability of WELLBUTRIN XL to both the immediate-release formulation and to the sustained-release formulation of bupropion under steady-state conditions, i.e., WELLBUTRIN XL 300 mg once daily was shown to have bioavailability that was similar to that of 100 mg 3 times daily of the immediate-release formulation of bupropion and to that of 150 mg 2 times daily of the sustained-release formulation of bupropion, with regard to both peak plasma concentration and extent of absorption, for parent drug and metabolites. Further, it has been demonstrated that Aplenzin is bioequivalent to WELLBUTRIN XL.

16 HOW SUPPLIED/STORAGE AND HANDLING

Aplenzin® Extended-Release Tablets, 174 mg of bupropion hydrobromide, are white to off white, round tablets printed with "BR" over "174" in bottles of 30 tablets (NDC 0024-5810-30).

Aplenzin® Extended-Release Tablets, 348 mg of bupropion hydrobromide, are white to off white, round tablets printed with "BR" over "348" in bottles of 30 tablets (NDC 0024-5811-30).

Aplenzin® Extended-Release Tablets, 522 mg of bupropion hydrobromide, are white to off white, round tablets printed with "BR" over "522" in bottles of 30 tablets (NDC 0024-5812-30).

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved Medication Guide below.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Aplenzin and should counsel them in its appropriate use.

A patient Medication Guide [see below**]** about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions," "Quit Smoking, Quit-Smoking Medications, Changes in Thinking and Behavior,"and other important information about using Aplenzin is available for Aplenzin. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Aplenzin.

Clinical Worsening and Suicide Risk in Treating Psychiatric Disorders: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation: Although Aplenzin is not indicated for smoking cessation treatment, it contains the same active ingredient as ZYBAN which is approved for this use. Patients should be informed that quitting smoking, with or without ZYBAN, may be associated with nicotine withdrawal symptoms (including depression or agitation), or exacerbation of pre-existing psychiatric illness. Furthermore, some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in behavior, that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

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

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

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

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

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

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

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

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