Brand Names

Aplenzin, Budeprion SR , Budeprion XL , Buproban, Forfivo XL, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban

Indication Specific Dosing

General Dosing Information
Converting from another bupropion formulation to Forfivo XL
Forfivo XL may be used in persons who are receiving 300 mg/day of another bupropion formulation for at least 2 weeks, and now require a dosage of 450 mg/day. Persons who are currently being treated with other bupropion products at 450 mg/day may be switched to an equivalent dose of Forfivo XL.

For the treatment of major depression

Oral dosage (immediate-release bupropion hydrochloride tablets; e.g., Wellbutrin)

Adults

100 mg PO twice daily, initially. May increase the dose to 100 mg PO 3 times daily after 3 days, and then up to 450 mg/day after several weeks if inadequate response. Max: 450 mg/day and 150 mg/dose.

Children† and Adolescents† 6 to 17 years

1.4 to 6 mg/kg/day PO, titrated upward slowly and administered in divided doses. Usual dose: 3 mg/kg/day. Max: 250 to 300 mg/day.

Oral dosage (sustained-release bupropion hydrochloride tablets; e.g., Wellbutrin SR)

Adults

150 mg PO once daily, initially. May increase the dose to 150 mg PO twice daily

after 3 days, and then 200 mg PO twice daily after several weeks if inadequate response. Max: 400 mg/day.

Adolescents†

2 mg/kg/dose (Max: 100 mg/dose) PO once daily for 2 to 3 weeks, initially. May increase the dose to 3 mg/kg/dose (Max:150 mg/dose) PO once daily for 2 to 3 weeks, then 3 mg/kg/dose (Max: 150 mg/dose) PO every morning and 2 mg/kg/dose (Max: 150 mg/dose) PO every evening for 2 to 3 weeks, and then 3 mg/kg/dose (Max: 150 mg/dose) PO twice daily if inadequate response. Alternately, 100 mg PO once daily for 1 week, initially. May increase the dose to 150 mg PO once daily for 2 weeks, then 150 mg PO twice daily for 1 to 3 weeks, and then 200 mg PO twice daily if inadequate response.

Oral dosage (extended-release bupropion hydrochloride tablets for once-daily administration; e.g., Wellbutrin XL)

Adults

150 mg PO once daily, initially. May increase the dose to 300 mg PO once daily after at least 4 days if inadequate response. Max: 450 mg/day. Taper dose to discontinue.

Oral dosage (extended-release bupropion hydrobromide tablets; e.g., Aplenzin) for bupropion-naive persons

Adults

174 mg PO once daily in the morning, initially. After 4 days, may increase to the target dose of 348 mg PO once daily in the morning.

Oral dosage (extended-release bupropion hydrobromide tablets; e.g., Aplenzin) for conversion from bupropion hydrochloride

Adults

174 mg bupropion hydrobromide PO once daily for 150 mg/day bupropion hydrochloride, 348 mg bupropion hydrobromide PO once daily for 300 mg/day bupropion hydrochloride, and 522 mg bupropion hydrobromide PO once daily for 450 mg/day bupropion hydrochloride. Give doses in the morning.

For the prevention of seasonal major depressive episodes associated with seasonal affective disorder (SAD)

Oral dosage (extended-release bupropion hydrochloride tablets; e.g., Wellbutrin XL)

Adults

Initiate in the autumn prior to the onset of depressive symptoms with 150 mg PO once daily in the morning. After 7 days, the dose may be increased to the target dose of 300 mg PO once daily in the morning if tolerated. Continue through the winter season. Taper and discontinue in early spring. For patients receiving 300 mg/day, taper to 150 mg/day prior to discontinuation. Total daily doses above 300 mg/day PO were not evaluated in seasonal affective disorder (SAD) trials. The start and duration of treatment should be individualized based on the patient's historical pattern of seasonal major depressive episodes. Patients whose seasonal depressive episodes are infrequent or not associated with significant impairment should not generally be treated prophylactically.

Oral dosage (extended-release bupropion hydrobromide; i.e., Aplenzin)

Adults

Initially, 174 mg PO once daily in the morning. After 7 days, the dose may be increased to the target dose of 348 mg PO once daily. Total daily doses above 348 mg/day PO were not evaluated in clinical trials for seasonal affective disorder (SAD). Treatment should be individualized based upon the patient's pattern of seasonal major depressive disorder (MDD) episodes. For prevention of seasonal MDD episodes associated with SAD, initiate therapy in the autumn prior to the onset of depressive symptoms. Continue through winter, then taper and discontinue in early spring. For patients receiving 348 mg/day, the dose should be tapered to 174 mg/day before discontinuation.

For tobacco cessation (smoking cessation) as an adjunct to psychosocial interventions

Oral dosage (sustained-release bupropion hydrochloride; e.g., Zyban)

Adults

150 mg PO once daily for 3 days, then 150 mg PO twice daily, at least 8 hours apart, for 7 to 12 weeks. Max: 300 mg/day. Initiate bupropion 1 to 2 weeks before the target quit date. Longer durations may be considered in individuals who quit

smoking but do not feel ready to discontinue bupropion therapy. VA/DoD guidelines suggest extending use beyond 12 weeks to maintain abstinence.

Adolescents†

150 mg PO once daily for 3 days, then 150 mg PO twice daily for 6 weeks. Max: 300 mg/day. Initiate bupropion 1 to 2 weeks before the target quit date. VA/DoD guidelines suggest extending use beyond 12 weeks to maintain abstinence.

For the treatment of attention-deficit hyperactivity disorder (ADHD)†

For the treatment of ADHD as monotherapy in adults†

Oral dosage (sustained-release; e.g., Wellbutrin SR)

Adults 18 to 64 years

150 mg PO once daily in the morning, initially. Increase the dose to 300 mg/day in 2 divided doses over 2 weeks. Doses of bupropion SR must be given at least 8 hours apart.

Oral dosage (extended-release; e.g., Wellbutrin XL)

Adults 18 to 64 years

150 mg PO once daily in the morning for at least 1 week, initially. Increase the dose to 300 mg PO once daily during weeks 2 to 4. May further increase the dose at approximately 8 weeks based on clinical response and tolerability. Max: 450 mg PO once daily.

For the treatment of ADHD as an alternative in children and adolescents†

Oral dosage (immediate-release; e.g., Wellbutrin)

Children and Adolescents 6 to 17 years

1.4 to 3 mg/kg/day PO in divided doses, initially. Increase the dose slowly. Average effective dose: 3 mg/kg/day. Max: 6 mg/kg/day or 150 to 300 mg/day. Limited data compared to other treatments; guidelines do not routinely recommend use in pediatric populations. Bupropion has been considered an alternative for some when other FDA-approved treatments have failed. A systematic review of available data found that bupropion had general efficacy comparable to methylphenidate but due to limited trial and effect sizes, more

data are needed. Some published data suggest potential efficacy in ADHD with comorbid conditions (e.g., conduct, substance use, or depressive disorders).

For the symptomatic treatment of neuropathic pain† due to various causes, including pain associated with peripheral diabetic neuropathy† or postherpetic neuralgia†

Oral dosage (sustained-release bupropion HCl tablets; e.g., Wellbutrin SR)

Adults

150 to 300 mg/day PO, given in 2 divided doses, was reported effective in one trial. Pain relief was noted to begin at week 2 of treatment, with 73% of patients receiving bupropion reporting improvement in pain vs. 10% with placebo.

For the treatment of cocaine dependence†

Oral dosage (immediate-release bupropion hydrochloride tablets; e.g., Wellbutrin)

Adults

Initially, 100 mg PO twice daily. May increase to 100 mg PO 3 times per day after 3 days, if tolerated. One guideline suggests considering the use of bupropion to promote cocaine abstinence. Bupropion may be particularly helpful for patients with concomitant nicotine dependence or co-occurring depressive disorders (low certainty, conditional recommendation).

Oral dosage (sustained-release bupropion hydrochloride tablets; e.g., Wellbutrin SR)

Adults

Initially, 150 mg PO once daily. May increase to 150 mg PO twice daily after 3 days, if tolerated. One guideline suggests considering the use of bupropion to promote cocaine abstinence. Bupropion may be particularly helpful for patients with concomitant nicotine dependence or co-occurring depressive disorders (low certainty, conditional recommendation).

Oral dosage (extended-release bupropion hydrochloride tablets for once-daily administration; e.g., Wellbutrin XL)

Adults

Initially, 150 mg PO once daily. May increase to 300 mg PO once daily after at least 4 days, if tolerated. One guideline suggests considering the use of bupropion to promote cocaine abstinence. Bupropion may be particularly helpful for patients with concomitant nicotine dependence or co-occurring depressive disorders.

For the treatment of amphetamine-type stimulant use disorder†

For treatment as monotherapy†

Oral dosage (sustained-release bupropion hydrochloride tablets; e.g., Wellbutrin SR)

Adults

Initially, 150 mg PO once daily. May increase to 150 mg PO twice daily after 3 days, if tolerated. Doses of 300 mg/day were shown to have a modest effect in reducing amphetamine-type stimulant use in patients with low- to moderate-frequency stimulant use (i.e., less than 18 days per month). One guideline suggests bupropion may be particularly useful for patients with concomitant tobacco use disorder or co-occurring depressive disorders (low certainty, conditional recommendation).

Oral dosage (extended-release bupropion hydrochloride tablets for once-daily administration; e.g., Wellbutrin XL)

Adults

Initially, 150 mg PO once daily. May increase to 300 mg PO once daily after at least 4 days, if tolerated. Doses of 300 mg/day were shown to have a modest effect in reducing amphetamine-type stimulants in patients with low- to moderate-frequency use (i.e., less than 18 days per month). One guideline suggests bupropion may be particularly useful for patients with concomitant tobacco use disorder or co-occurring depressive disorders (low certainty, conditional recommendation).

For treatment in combination with injectable naltrexone†

Oral dosage (extended-release bupropion hydrochloride tablets for once-daily administration; e.g., Wellbutrin XL)

Adults

Initially, 150 mg PO once daily. After at least 4 days of dosing, may increase to

300 mg/day. Max: 450 mg/day, after appropriate titration. When given in combination with injectable naltrexone (380 mg IM every 3 to 4 weeks), bupropion appears to promote a reduction in use of amphetamine-type stimulants. In small studies of individuals with moderate or severe methamphetamine use disorder, this combination was shown to reduce methamphetamine use compared to placebo. One guideline suggests this combination may be particularly helpful for individuals with comorbid alcohol use disorder, as naltrexone has been shown to be helpful in reducing alcohol consumption. Bupropion may be helpful for individuals with comorbid tobacco use or depressive disorders (moderate certainty, conditional recommendation).

Contraindications And Precaution

Drug Interactions

The coadministration of certain medications may lead to harm and require avoidance or therapy modification; review all drug interactions prior to concomitant use of other medications.

Hypersensitivity

This medication is contraindicated in patients with a history of hypersensitivity to it or any of its components.

anorexia nervosa, brain injury, bulimia nervosa, cerebral arteriovenous malformation, CNS infection, CNS tumor, diabetes mellitus, hypoglycemia, hyponatremia, hypoxia, seizure disorder, stroke, substance abuse disorder

Bupropion is contraindicated in people with a seizure disorder or conditions that increase the risk of seizures (e.g., severe head injury or brain injury, cerebral arteriovenous malformation, CNS tumor, CNS infection, severe stroke, anorexia nervosa, bulimia nervosa, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic medications). Bupropion should be used with caution in conditions that can increase the risk of seizure, including use of concomitant medications that lower the seizure threshold, metabolic disorders (e.g. hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), or a substance abuse disorder [the use of illicit drugs (e.g., cocaine) or the abuse or misuse of prescription medications (e.g., CNS stimulants)]. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic medications or insulin, the use of anorectic drugs, and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

adolescents, children, suicidal ideation

All patients receiving antidepressants should be monitored closely for clinical worsening, suicidal ideation, and unusual changes in mood or behavior, especially at treatment initiation or after dose changes. Instruct caregivers and patients to immediately notify the prescriber of changes in behavior or suicidal ideation. A change to the treatment regimen or discontinuation of bupropion may be necessary in patients with emerging suicidality or worsening depression. In a pooled analysis of placebo-controlled trials of antidepressants (n = 4,500 pediatrics and 77,000 adults), there was an increased risk for suicidal thoughts and behaviors in children, adolescents, and young adult patients 24 years of age and younger receiving an antidepressant versus placebo, with considerable variation in the risk of suicidality among drugs. The difference in absolute risk of suicidal thoughts and behaviors across different indications was highest in those with major depression. No suicides occurred in any of the pediatric trials. Nevertheless, the need for an antidepressant in children, adolescents, or young adults for any use must be weighed against the risk of suicidality; it is unknown if this risk extends to long-term use.

Tourette syndrome

Individuals with tics or Tourette syndrome should be closely monitored for emerging or worsening tics during treatment with bupropion. Like other stimulant medications, bupropion may precipitate or exacerbate motor or phonetic tics in these conditions.

bipolar disorder, major psychiatric disorder

Activation of mania, hypomania, or a mixed episode may occur with medications used to treat depression, especially in people predisposed to bipolar disorder. A major depressive episode may be the initial presentation of bipolar disorder. Prior to initiating treatment with bupropion, people with depressive symptoms should be screened for risk factors for bipolar disorder, including a detailed personal psychiatric history and family history of bipolar disorder, suicide, and/or depression. If an individual taking bupropion develops symptoms consistent with mania or hypomania, the medication should be discontinued, and appropriate therapy should be initiated. Patients taking bupropion for smoking cessation should be monitored closely for development of neuropsychiatric adverse events, particularly in individuals with a pre-existing major psychiatric disorder (e.g., schizophrenia, depression, bipolar disorder). Serious neuropsychiatric adverse effects were reported in postmarketing use of bupropion for smoking cessation. Advise patients and caregivers to stop bupropion and contact their 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. The provider should evaluate symptom severity and the extent of benefits from treatment, and consider dose reduction or

discontinuation, or continued treatment with closer monitoring. In many cases, resolution of symptoms has occurred after discontinuation, although the symptoms can persist; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

Child-Pugh class A, Child-Pugh class B, Child-Pugh class C, hepatic failure

Forfivo XL, a 450 mg extended-release tablet formulation of bupropion, is not recommended in people with hepatic impairment because a lower dosage strength is not available for use in this patient population. For other bupropion formulations, the dosage or dosage frequency should be reduced in patients with moderate to severe hepatic impairment (Child-Pugh class B, child-Pugh class C) or hepatic failure. For patients with mild hepatic dysfunction (Child-Pugh class A), reduced dosage or dosage frequency should be considered; however, no specific guidelines are available. Monitor patients with any degree of hepatic dysfunction carefully. Bupropion undergoes extensive hepatic metabolism and excretion in the urine as metabolites; there is a risk for accumulation in hepatic impairment. In addition, caution is advisable when using bupropion in people with severe hepatic impairment because this condition can increase the risk of seizures.

renal failure, renal impairment

Forfivo XL, a 450 mg extended-release tablet formulation of bupropion, is not recommended in people with renal impairment since a lower dosage strength is not available for use in this patient population. Other bupropion products should be used with caution in patients with renal impairment or renal failure because the parent compound or active metabolites could accumulate. Consider reduced doses or a change in dosing frequency in these patient populations, and closely monitor for adverse reactions that could indicate high drug or metabolite levels.

cardiac disease, hypertension

Treatment with bupropion can result in elevated blood pressure and hypertension or may exacerbate pre-existing hypertension. Caution is advised when administering bupropion to people with pre-existing hypertension or in those who are sensitive to changes in blood pressure. There are no controlled studies assessing the safety of bupropion in people with a recent history of myocardial infarction or unstable cardiac disease. Blood pressure should be assessed prior to initiating bupropion and monitored periodically throughout treatment. Risks of hypertension may be increased in people taking bupropion in combination with nicotine transdermal systems for smoking

cessation; monitor these patients for treatment-emergent hypertension. Bupropion has been used off-label for the treatment of attention-deficit hyperactivity disorder (ADHD) in pediatric patients. The American Heart Association recommends conducting a detailed patient and family history and physical examination prior to initiating bupropion in pediatric patients, and to consider obtaining a baseline electrocardiogram (ECG).

activities requiring coordination and concentration, driving or operating machinery

Bupropion has the potential to impair judgment, thinking, or motor skills. Patients should use caution when driving or operating machinery or participating in other activities requiring coordination and concentration until they are reasonably certain that bupropion does not affect them adversely. Bupropion use may decrease alcohol tolerance; the consumption of alcohol during treatment with bupropion should be minimized or avoided.

closed-angle glaucoma, narrow iridocorneal angles

Caution is recommended when prescribing bupropion to patients with closed-angle glaucoma. The pupillary dilation that can occur with antidepressants may precipitate a closed-angle glaucoma attack in patients with anatomically narrow iridocorneal angles who do not have a patent iridectomy.

geriatric

No overall differences in safety or effectiveness were observed between geriatric and younger subjects during clinical trials of bupropion for depression or smoking cessation, respectively. The risk of adverse reactions may be greater in older adults with impaired renal function and it may be necessary to consider renal function in dose selection in this population The U.S. Omnibus Budget Reconciliation Act (OBRA) regulates antidepressant use in long-term care facilities. When used to manage behavior, stabilize mood, or treat a psychiatric disorder, tapering as outlined in the OBRA guidelines should be attempted unless clinically contraindicated. Dosages and durations of treatment should align with prescribing labels, published literature recommendations, and expert guidelines.

pregnancy

Use bupropion with caution during pregnancy. When treating a pregnant person, the care team should carefully consider the potential risks and benefits of treatment. Consider the risks to the pregnant person of untreated depression and potential effects

on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum. Pregnant people who smoke should be encouraged to attempt educational and behavioral interventions before pharmacologic approaches are used; nicotine has been used in pregnancy to help patients quit smoking. Smoking cessation programs in pregnancy reduce the proportion of people who continue to smoke and reduces the risk for low birthweight and preterm birth. Data from epidemiological studies including pregnant people exposed to bupropion in the first trimester indicate no increased risk of congenital malformations. In addition, no increased risk of cardiovascular malformations during first trimester exposure to bupropion has been observed. The rate of cardiovascular malformations following 675 exposures to bupropion in the first trimester was 1.3% versus a background rate of about 1%. Data collected from the United Healthcare database and the National Birth Defects Prevention Study (NBDPS) (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) did not show an overall increased risk of cardiovascular malformations after bupropion exposure during the first trimester. Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO, and the Slone Epidemiology case control study did not find increased risk for LVOTO. Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17) but did not find increased risk for any other cardiovascular malformations studied, including LVOTO. The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD. For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case-control studies. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits. However, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to or more than the maximum recommended human dose (MRHD) and decreased fetal weights were seen at doses twice the MRHD and greater. There is a pregnancy exposure registry that monitors outcomes in pregnant patients exposed to bupropion; information about the registry can be obtained at womensmentalhealth.org/research/pregnancyregistry/antidepressants or by calling 1-844-405-6185.

breast-feeding

Use bupropion with caution during breast-feeding. Bupropion and its metabolites are excreted into human milk. In one lactation study (n = 10), the average daily infant exposure to bupropion and its active metabolites (assuming 150 mL/kg daily human milk consumption) was 2% of the maternal weight-adjusted dose. Limited data from postmarketing reports have not identified a clear association of adverse reactions in the breast-fed child. Postmarketing reports have described seizures in breast-fed infants; the relationship between seizures in the breast-fed child and maternal bupropion use is unclear. Peak breast milk concentrations of bupropion and its metabolites are present within 2 to 4 hours after an oral dose. One case report describes a possible seizure in a breast-fed infant during maternal use of extended-release bupropion. In 2 other cases, no infant-related adverse events were noted during breast-feeding. Due to individual variability in response to antidepressants, it may be prudent to continue the existing regimen if ongoing treatment for depression is deemed necessary during breast-feeding. Alternatives may be considered in some cases. A pooled analysis found that maternal use of sertraline, along with nortriptyline and paroxetine, usually produced undetectable or low drug concentrations in infant serum. These agents may be the preferred antidepressants when initiating antidepressant therapy in a breast-feeding person. For smoking cessation treatment, nicotine replacement products may be considered as an alternate therapy for bupropion if non-pharmacologic interventions are inadequate. The decision of whether to use nicotine replacement therapy in a person who is breast-feeding should be evaluated in comparison to the risks associated with exposure of the infant to nicotine and other tobacco contaminants in the breast milk as well as those of passive exposure to tobacco smoke. Breast-feeding and eliminating an infant's exposure to tobacco smoke are considered important protective factors for serious pediatric health risks.

Pregnancy And Lactation

Use bupropion with caution during pregnancy. When treating a pregnant person, the care team should carefully consider the potential risks and benefits of treatment. Consider the risks to the pregnant person of untreated depression and potential effects on the fetus when discontinuing or changing treatment with antidepressant medications during pregnancy and postpartum. Pregnant people who smoke should be encouraged to attempt educational and behavioral interventions before pharmacologic approaches are used; nicotine has been used in pregnancy to help patients quit smoking. Smoking cessation programs in pregnancy reduce the proportion of people who continue to smoke and reduces the risk for low birthweight and preterm birth. Data from epidemiological studies including pregnant people exposed to bupropion in the first trimester indicate no increased risk of congenital malformations. In addition, no

increased risk of cardiovascular malformations during first trimester exposure to bupropion has been observed. The rate of cardiovascular malformations following 675 exposures to bupropion in the first trimester was 1.3% versus a background rate of about 1%. Data collected from the United Healthcare database and the National Birth Defects Prevention Study (NBDPS) (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) did not show an overall increased risk of cardiovascular malformations after bupropion exposure during the first trimester. Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO, and the Slone Epidemiology case control study did not find increased risk for LVOTO. Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17) but did not find increased risk for any other cardiovascular malformations studied, including LVOTO. The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD. For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case-control studies. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits. However, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately equal to or more than the maximum recommended human dose (MRHD) and decreased fetal weights were seen at doses twice the MRHD and greater. There is a pregnancy exposure registry that monitors outcomes in pregnant patients exposed to bupropion; information about the registry can be obtained at womensmentalhealth.org/research/pregnancyregistry/antidepressants or by calling 1-844-405-6185.

Interactions

Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and

some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Acetaminophen; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Acetaminophen; Caffeine; Dihydrocodeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy. (Moderate) Concomitant use of dihydrocodeine with bupropion may increase dihydrocodeine plasma concentrations, but decrease the plasma concentration of the active metabolite, dihydromorphine, resulting in reduced efficacy or symptoms of opioid withdrawal. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of dihydrocodeine until stable drug effects are achieved. Discontinuation of bupropion could decrease dihydrocodeine plasma concentrations and increase dihydromorphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Dihydrocodeine is primarily metabolized by CYP2D6 to dihydromorphine, and by CYP3A4. Bupropion is a strong inhibitor of CYP2D6.
Acetaminophen; Caffeine; Pyrilamine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and

beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Acetaminophen; Chlorpheniramine; Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Acetaminophen; Codeine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Acetaminophen; Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects.

Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Dextromethorphan; Doxylamine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Dextromethorphan; guaiFENesin; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Dextromethorphan; guaiFENesin; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Acetaminophen; Dextromethorphan; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Acetaminophen; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Acetaminophen; HYDROcodone: (Moderate) Concomitant use of hydrocodone with

bupropion may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of bupropion could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If bupropion is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP2D6. Bupropion is a strong inhibitor of CYP2D6.
Acetaminophen; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
acetaZOLAMIDE: (Moderate) It should be noted that when anticonvulsants are used for the purpose of treating epilepsy (versus use in mood disorders or neuropathic pain or other non-epilepsy conditions), that bupropion should not be used by patients with a preexisting seizure disorde; this represents a disease-drug interaction, and not a drug-drug interaction per se. Bupropion may be combined with anticonvulsant treatments with caution when an anticonvulsant is used for non-epilepsy conditions. Addiive CNS effects are possible, and the patient may feel dizzy, drowsy or more tired when taking these drugs together.
Albuterol; Budesonide: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
ALFentanil: (Moderate) If concomitant use of alfentanil and bupropion is warranted, monitor patients for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Alosetron: (Moderate) Alosetron, if used with drugs that have anticholinergic effects such as bupropion, may seriously worsen constipation, leading to events such as GI obstruction/impaction or paralytic ileus. Although specific recommendations are not available from the manufacturer, it would be prudent to avoid these drugs in patients taking alosetron.
Amantadine: (Major) Use caution when concurrently administering bupropion and amantadine; if concurrent use is necessary, low initial dosing and slow dosage titration of bupropion should be considered. Both bupropion and amantadine have dopamine agonist effects, and coadministration may result in additive CNS dopaminergic effects. Reported adverse reactions have included neurologic side effects such as restlessness,

agitation, gait disturbance, vertigo, and dizziness; some patients have required hospitalization. In reported cases, discontinuation of the drugs resulted in symptom resolution.
Amifampridine: (Major) Carefully consider the need for concomitant treatment with bupropion and amifampridine, as coadministration may increase the risk of seizures. Consider alternatives to bupropion. If use together is medically necessary, closely monitor patients for seizure activity. Seizures have been observed in patients without a history of seizures taking amifampridine at recommended doses. Bupropion is known to have a dose-dependent risk for seizures.
Amitriptyline: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Amobarbital: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Amoxapine: (Major) Concurrent administration of amoxapine with bupropion should be undertaken only with extreme caution due to the potential for increased risk of seizures from the lowering of seizure threshold. In addition, bupropion inhibits the hepatic isozyme CYP2D6 and thus may reduce the clearance of amoxapine leading to a potential for increased Cmax, AUC and half-life. Amoxapine appears to be metabolized via CYP2D6. Low initial dosing and gradual dose increases of both drugs should be employed. If bupropion is added to a regimen of a patient already receiving amoxapine, the need to reduce the amoxapine dosage should be considered.
Amphetamine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including amphetamine; dextroamphetamine. Use low initial doses of bupropion and increase the dose gradually.
Amphetamine; Dextroamphetamine Salts: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as

stimulants including amphetamine; dextroamphetamine. Use low initial doses of bupropion and increase the dose gradually.
Amphetamine; Dextroamphetamine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including amphetamine; dextroamphetamine. Use low initial doses of bupropion and increase the dose gradually.
ARIPiprazole: (Major) Recommendations for managing aripiprazole and bupropion vary by aripiprazole dosage form. For aripiprazole oral dosage forms, administer half of the usual dose. For monthly extended-release aripiprazole injections (Abilify Maintena), reduce the dosage from 400 mg to 300 mg/month or from 300 mg to 200 mg/month. For extended-release aripiprazole injections given once every 2 months (Abilify Asimtufii), reduce the dosage from 960 mg to 720 mg. Further dosage reductions may be required in patients who are also receiving a CYP3A inhibitor; see individual product prescribing information for details. Concomitant use may increase aripiprazole exposure and risk for side effects. Aripiprazole is CYP2D6 and CYP3A substrate; bupropion is a strong CYP2D6 inhibitor. (Major) Recommendations for managing aripiprazole and bupropion vary by aripiprazole dosage form. For extended-release aripiprazole lauroxil injections (Aristada), reduce the dose to the next lowest strength; no dosage adjustment is required for patients tolerating 441 mg or for patients known to be poor metabolizers of CYP2D6. For fixed dose extended-release aripiprazole lauroxil injections (Aristada Initio), avoid concomitant use because the dose cannot be modified. Further dosage reductions may be required in patients who are also receiving a CYP3A inhibitor; see individual product prescribing information for details. Concomitant use may increase aripiprazole exposure and risk for side effects. Aripiprazole is CYP2D6 and CYP3A substrate; bupropion is a strong CYP2D6 inhibitor.
Armodafinil: (Major) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including non-prescription stimulants and weight loss medications, is associated with an increased seizure risk; seizures may be more likely to occur in these patients during concurrent use of bupropion. Patients should be closely monitored if these combinations are necessary.
Asenapine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
Aspirin, ASA; Butalbital; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and

seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy. (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Aspirin, ASA; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Aspirin, ASA; Caffeine; Orphenadrine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged

opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Atazanavir; Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Atomoxetine: (Major) Dosage reduction of atomoxetine is recommended in patients receiving bupropion due to the potential for increased atomoxetine exposure and related adverse effects. In children and adolescents up to 70 kg receiving bupropion, atomoxetine should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well-tolerated. In children and adolescents over 70 kg and adults receiving bupropion, atomoxetine should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well-tolerated. Bupropion is a strong CYP2D6 inhibitor; atomoxetine is a CYP2D6 substrate. Coadministration of a strong CYP2D6 inhibitor and atomoxetine in extensive metabolizers of CYP2D6, increased atomoxetine steady-state plasma concentrations by approximately 6 to 8-fold. This increase is similar to exposures observed in poor metabolizers. Concurrent use of a strong CYP2D6 inhibitor with atomoxetine in poor metabolizers is not expected to increase atomoxetine exposure.
Atropine: (Moderate) The anticholinergic effects of atropine may be enhanced when combined with other drugs with moderate to significant anticholinergic effects including bupropion. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Atropine; Difenoxin: (Moderate) The anticholinergic effects of atropine may be enhanced when combined with other drugs with moderate to significant anticholinergic effects including bupropion. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Azelastine; Fluticasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Barbiturates: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it

may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Beclomethasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Contraindicated) Due to an increased risk of hypertensive reactions, treatment initiation with bupropion is contraindicated in patients currently receiving intravenous methylene blue. If urgent psychiatric treatment is required, interventions other than bupropion (e.g., alternative medication, hospitalization) should be considered. Conversely, in patients receiving bupropion and requiring urgent treatment with intravenous methylene blue, bupropion should be discontinued immediately and methylene blue therapy initiated only if acceptable alternatives are not available and the potential benefits of methylene blue outweigh the risks. The patient should be monitored for hypertensive reactions for two weeks or until 24 hours after the last dose of methylene blue, whichever comes first. Bupropion may be re-initiated 24 hours after the last dose of methylene blue. It is not known if administration of methylene blue by other routes (e.g., orally, local injection) or in doses less than 1 mg/kg IV can produce a similar outcome. (Moderate) Additive anticholinergic effects may be seen when hyoscyamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Benzphetamine: (Major) The risk of seizures from the use of bupropion may be increased with concomitant use of CNS stimulants and anorectics that may induce seizures, including benzphetamine. Concurrent use is not recommended. Extreme caution and close clinical monitoring is recommended if these agents must be used together.
Benztropine: (Moderate) Additive anticholinergic effects may be seen when benztropine is used concomitantly with other drugs that possess anticholinergic properties, such as bupropion. Clinicians should note that anticholinergic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Betamethasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Bethanechol: (Moderate) Bupropion exhibits moderate anticholinergic properties. Avoid

co-use when possible since the effects of bethanechol, a cholinergic agonist, may be diminished. If co-use is necessary, monitor for the intended clinical response.
Brexpiprazole: (Major) Because brexpiprazole is primarily metabolized by CYP3A4 and CYP2D6, the manufacturer recommends that the brexpiprazole dose be reduced to one-half of the usual dose in patients receiving a strong CYP2D6 inhibitor and one-quarter (25%) of the usual dose in patients receiving a moderate to strong inhibitor of CYP3A4 in combination with a moderate to strong inhibitor of CYP2D6. Bupropion is a strong inhibitor of CYP2D6. If these agents are used in combination, the patient should be carefully monitored for brexpiprazole-related adverse reactions. Additionally, bupropion is associated with a dose-related increase in seizures; antipsychotics may increase this risk. It should be noted that no dosage adjustment is needed in patients taking a strong CYP2D6 inhibitor who are receiving brexpiprazole as adjunct treatment for major depressive disorder because CYP2D6 considerations are already factored into general dosing recommendations.
Brimonidine; Timolol: (Minor) Monitor for an increased incidence of timolol-related adverse effects if bupropion and timolol are used concomitantly. Coadministration of bupropion and timolol may result in increased plasma concentrations of timolol. Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Timolol is a CYP2D6 substrate.
Brompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Brompheniramine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Brompheniramine; Pseudoephedrine; Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Budesonide: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic

corticosteroids, increases the seizure risk.
Budesonide; Formoterol: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Budesonide; Glycopyrrolate; Formoterol: (Moderate) Additive anticholinergic effects may be seen when glycopyrrolate is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Buprenorphine: (Moderate) If concomitant use of buprenorphine and bupropion is warranted, monitor patients for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Buprenorphine; Naloxone: (Moderate) If concomitant use of buprenorphine and bupropion is warranted, monitor patients for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Butalbital; Acetaminophen: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Butalbital; Acetaminophen; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive

caffeine intake during bupropion therapy. (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Butalbital; Acetaminophen; Caffeine; Codeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy. (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Butalbital; Aspirin; Caffeine; Codeine: (Moderate) Bupropion is associated with a dose-

related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy. (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Caffeine; Sodium Benzoate: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an

increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during bupropion therapy.
Calcium, Magnesium, Potassium, Sodium Oxybates: (Major) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as sodium oxybate. The risk of seizures with bupropion is dose related and is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment If used together, use low initial doses of bupropion and increase the dose gradually.
Cannabidiol: (Moderate) Consider a dose adjustment of bupropion when coadministered with cannabidiol. Coadministration may alter plasma concentrations of bupropion resulting in an increased risk of adverse reactions and/or decreased efficacy. Bupropion is a substrate of CYP2B6; cannabidiol may inhibit and/or induce CYP2B6 at clinically relevant concentrations.
carBAMazepine: (Moderate) Monitor for reduced bupropion efficacy during coadministration of carbamazepine as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose. Avoid concomitant use of combination dextromethorphan; bupropion and carbamazepine. Bupropion is a CYP2B6 substrate and carbamazepine is a strong CYP2B6 inducer. Concomitant use was observed to decrease bupropion overall exposure by 76% and dextromethorphan overall exposure by 64%.
Carbidopa; Levodopa: (Moderate) Monitor for symptoms of CNS toxicity, such as restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness, if concomitant use of levodopa and bupropion is necessary. Both medications have dopamine agonist effects and use may increase the risk for dopamine-related adverse reactions.
Carbidopa; Levodopa; Entacapone: (Moderate) Monitor for symptoms of CNS toxicity, such as restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness, if concomitant use of levodopa and bupropion is necessary. Both medications have dopamine agonist effects and use may increase the risk for dopamine-related adverse reactions.
Cariprazine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be

used; the patient should be closely monitored.
Carvedilol: (Minor) Monitor for an increased incidence of carvedilol-related adverse effects if bupropion and carvedilol are used concomitantly. Coadministration of bupropion and carvedilol may result in increased plasma concentrations of carvedilol. Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Carvedilol is a CYP2D6 substrate.
Celecoxib; Tramadol: (Moderate) Monitor for reduced efficacy of tramadol, signs of opioid withdrawal, seizures, or serotonin syndrome if coadministration with bupropion is necessary. If bupropion is discontinued, consider a dose reduction of tramadol and frequently monitor for signs of respiratory depression and sedation. Tramadol is a CYP2D6 substrate and bupropion is a CYP2D6 inhibitor. Concomitant use of tramadol with CYP2D6 inhibitors can increase the plasma concentration of tramadol and decrease the plasma concentration of the active metabolite M1. Since M1 is a more potent mu-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who have developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Cenobamate: (Major) Increase the dosage of bupropion as needed when coadministered with cenobamate due to the potential for reduced efficacy of bupropion. Multiple doses of cenobamate decreased bupropion exposure by 39%. Bupropion is a sensitive substrate of CYP2B6; cenobamate is a weak CYP2B6 inducer.
Cetirizine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Cevimeline: (Moderate) Cevimeline is partially metabolized by CYP2D6. Inhibitors of this isoenzyme, like bupropion, would be expected to lead to an increase in cevimeline plasma concentrations.
Chlophedianol; Dexchlorpheniramine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
chlordiazePOXIDE; Amitriptyline: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider

discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
chlordiazePOXIDE; Clidinium: (Moderate) Bupropion exhibits moderate anticholinergic effects. Clinicians should consider this when using antimuscarinics and other medications with anticholinergic activity in combination with bupropion.
Chlorpheniramine; Codeine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Chlorpheniramine; Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Chlorpheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Chlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.

Chlorpheniramine; HYDROcodone: (Moderate) Concomitant use of hydrocodone with bupropion may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of bupropion could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If bupropion is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP2D6. Bupropion is a strong inhibitor of CYP2D6.
Chlorpheniramine; Ibuprofen; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Chlorpheniramine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
chlorproMAZINE: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of chlorpromazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of chlorpromazine may result in QT prolongation, somnolence, anticholinergic effects, or orthostasis.
Ciclesonide: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Citalopram: (Moderate) Monitor for an increase in the frequency and severity of citalopram-related adverse effects, such as QT prolongation and serotonin syndrome, during concomitant use of bupropion. Concomitant use has been observed to increase the peak and overall exposure of citalopram by 30% and 40%, respectively.
clomiPRAMINE: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants

are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Clopidogrel: (Moderate) Monitor for an increase in bupropion-related adverse reactions during coadministration of clopidogrel as concurrent use may increase bupropion exposure. A bupropion dose adjustment may be necessary. Bupropion is a sensitive substrate of CYP2B6; clopidogrel is a weak CYP2B6 inhibitor.
cloZAPine: (Major) Monitor for evidence of clozapine-related adverse reactions and consider a clozapine dose reduction if necessary when coadministered with bupropion. If bupropion is discontinued after dose adjustments are made, monitor for lack of clozapine affect and consider increasing the clozapine dose if necessary. Concurrent use may result in increased clozapine exposure due to inhibition of CYP2D6 metabolism by bupropion. Treatment with clozapine has been associated with QT prolongation, torsade de pointes (TdP), cardiac arrest, and sudden death. Elevated plasma concentrations of clozapine may potentially increase the risk of life-threatening arrhythmias, sedation, anticholinergic effects, seizures, orthostasis, or other adverse effects. Furthermore, bupropion is associated with a dose-related risk of seizures; this risk may be increased by antipsychotics.
Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Cocaine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as cocaine. This is of particular concern in those with excessive cocaine use (i.e., cocaine addition). Patients should be closely monitored if this combination is necessary.
Codeine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Codeine; Dexbrompheniramine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid

withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Codeine; guaiFENesin: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6.
Codeine; guaiFENesin; Pseudoephedrine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Codeine; Phenylephrine; Promethazine: (Moderate) Concomitant use of codeine with

bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as promethazine. Use low initial doses of bupropion and increase the dose gradually.
Codeine; Promethazine: (Moderate) Concomitant use of codeine with bupropion may increase codeine plasma concentrations, but decrease the plasma concentration of the active metabolite, morphine, resulting in reduced efficacy or symptoms of opioid withdrawal. It is recommended to avoid this combination when codeine is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage increase of codeine until stable drug effects are achieved. Discontinuation of bupropion could decrease codeine plasma concentrations and increase morphine plasma concentrations resulting in prolonged opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. If bupropion is discontinued, monitor the patient carefully and consider reducing the opioid dosage if appropriate. Codeine is primarily metabolized by CYP2D6 to morphine, and by CYP3A4 to norcodeine; norcodeine does not have analgesic properties. Bupropion is a strong inhibitor of CYP2D6. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as promethazine. Use low initial doses of bupropion and increase the dose gradually.
Corticosteroids: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Cortisone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Cyclobenzaprine: (Moderate) Use extreme caution when coadministering bupropion

with other drugs that lower the seizure threshold, such as cyclobenzaprine. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome.
Dabrafenib: (Major) The concomitant use of dabrafenib and bupropion may lead to decreased bupropion concentrations and loss of efficacy. Use of an alternative agent is recommended. If concomitant use of these agents is unavoidable, monitor patients for loss of bupropion efficacy. In vitro, dabrafenib is an inducer of CYP2B6 via activation of the pregnane X receptor and constitutive androstane receptor nuclear receptors. Bupropion is a sensitive CYP2B6 substrate.
Dalfampridine: (Moderate) Due to additive risks for seizure, extreme caution when coadministering bupropion with other drugs that lower seizure threshold (e.g., dalfampridine). Use low initial doses and increase the dose gradually. Monitor for seizure activity. Consider benefits against the risk of seizures. Consider alternatives to bupropion. Additionally, bupropion inhibits OCT2 in vitro, but the clinical relevance is not certain. Concurrent treatment with OCT2 inhibitors, such as bupropion, may cause increased exposure to dalfampridine. Elevated levels of dalfampridine increase the risk of seizures. The potential benefits of taking OCT2 inhibitors concurrently with dalfampridine should be considered against the risk of seizures in these patients.
Darifenacin: (Moderate) Bupropion, an inhibitor of CYP2D6 may inhibit the metabolism of darifenacin. In addition, bupropion is associated with moderate anticholinergic effects which could be additive when coadministered with darifenacin. Patients should be monitored for increased anticholinergic effects or other adverse effects when these two drugs are coadministered. Dosage adjustments may be necessary.
Darunavir; Cobicistat: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Deflazacort: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Desipramine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an

increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Desloratadine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Deutetrabenazine: (Major) Do not exceed 18 mg/dose or 36 mg/day of deutetrabenazine if must use concurrently with a strong CYP2D6 inhibitor. Bupropion is a strong CYP2D6 inhibitor, and the metabolites of deutetrabenazine, alpha- and beta-HTBZ, are CYP2D6 substrates. The systemic exposure of alpha- and beta-HTBZ may be increased resulting in an increase in deutetrabenazine-related adverse reactions, like QT prolongation and drowsiness.
dexAMETHasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Dexbrompheniramine; Dextromethorphan; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dexbrompheniramine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Dexchlorpheniramine; Dextromethorphan; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Dexmethylphenidate: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including methylphenidate. Use low initial doses of bupropion and increase the dose gradually.

Dextroamphetamine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including amphetamine; dextroamphetamine. Use low initial doses of bupropion and increase the dose gradually.
Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dextromethorphan; buPROPion: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dextromethorphan; diphenhydrAMINE; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dextromethorphan; guaiFENesin: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dextromethorphan; guaiFENesin; Phenylephrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dextromethorphan; guaiFENesin; Pseudoephedrine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme

caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Dextromethorphan; quiNIDine: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold.
Dicyclomine: (Moderate) Additive anticholinergic effects may be seen when dicyclomine is used concomitantly with other drugs that possess anticholinergic properties, such as bupropion. Clinicians should note that anticholinergic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Diethylpropion: (Major) Drugs which may lower the seizure threshold, such as diethylpropion, should be used with great caution or avoided in patients taking bupropion. The manufacturer recommends low initial dosing and slow dosage titration of bupropion if this combination must be used concurrently; the patient should be closely monitored.
Digoxin: (Moderate) Monitor plasma digoxin concentrations during concomitant bupropion use. Concomitant use may decrease plasma digoxin concentrations. Digoxin exposure was decreased when a single oral dose of digoxin 0.5 mg was administered 24 hours after a single oral dose of extended-release bupropion 150 mg in healthy volunteers.
Diphenoxylate; Atropine: (Moderate) The anticholinergic effects of atropine may be enhanced when combined with other drugs with moderate to significant anticholinergic effects including bupropion. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Dorzolamide; Timolol: (Minor) Monitor for an increased incidence of timolol-related adverse effects if bupropion and timolol are used concomitantly. Coadministration of bupropion and timolol may result in increased plasma concentrations of timolol. Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Timolol is a CYP2D6 substrate.
Doxepin: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin

syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Doxercalciferol: (Moderate) CYP450 enzyme inhibitors, like bupropion, may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if cytochrome P450 inhibitors are coadministered with doxercalciferol.
DOXOrubicin Liposomal: (Major) In vitro, bupropion is a mild CYP2D6 inhibitor and doxorubicin is a major CYP2D6 substrate. Clinically significant interactions have been reported when doxorubicin was coadministered with inhibitors of CYP2D6, resulting in increased concentration and clinical effect of doxorubicin. Avoid coadministration of bupropion and doxorubicin if possible. If not possible, closely monitor for increased side effects of doxorubicin including myelosuppression and cardiotoxicity.
DOXOrubicin: (Major) In vitro, bupropion is a mild CYP2D6 inhibitor and doxorubicin is a major CYP2D6 substrate. Clinically significant interactions have been reported when doxorubicin was coadministered with inhibitors of CYP2D6, resulting in increased concentration and clinical effect of doxorubicin. Avoid coadministration of bupropion and doxorubicin if possible. If not possible, closely monitor for increased side effects of doxorubicin including myelosuppression and cardiotoxicity.
DULoxetine: (Moderate) Monitor for increased duloxetine-related adverse effects if coadministered with bupropion. Concurrent use may result in increased duloxetine exposure. Duloxetine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Coadministration with another strong CYP2D6 inhibitor increased the duloxetine AUC by about 60%.
Dutasteride; Tamsulosin: (Moderate) Use caution if coadministration of bupropion with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Tamsulosin is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant treatment with another strong CYP2D6 inhibitor increased the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively.
Efavirenz: (Major) Concurrent use of efavirenz 600 mg/day and bupropion in healthy volunteers resulted in a reduction of the AUC and Cmax of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged and the Cmax of hydroxybupropion was increased by 50%. Healthcare providers are advised to increase the dose of bupropion based on clinical response during concurrent use with efavirenz; however, the maximum recommended dose of bupropion should not be exceeded.
Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate: (Major) Concurrent use of efavirenz 600 mg/day and bupropion in healthy volunteers resulted in a reduction of the

AUC and Cmax of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged and the Cmax of hydroxybupropion was increased by 50%. Healthcare providers are advised to increase the dose of bupropion based on clinical response during concurrent use with efavirenz; however, the maximum recommended dose of bupropion should not be exceeded.
Efavirenz; lamiVUDine; Tenofovir Disoproxil Fumarate: (Major) Concurrent use of efavirenz 600 mg/day and bupropion in healthy volunteers resulted in a reduction of the AUC and Cmax of bupropion by approximately 55% and 34%, respectively. The AUC of hydroxybupropion was unchanged and the Cmax of hydroxybupropion was increased by 50%. Healthcare providers are advised to increase the dose of bupropion based on clinical response during concurrent use with efavirenz; however, the maximum recommended dose of bupropion should not be exceeded.
Eliglustat: (Major) Reduce the dose of eliglustat to 84 mg once daily in patients who are extensive or intermediate CYP2D6 metabolizers (EMs or IMs) and receiving bupropion. Eliglustat is contraindicated in EMs and IMs who are receiving bupropion plus a strong or moderate CYP3A inhibitor. Eliglustat is contraindicated in poor metabolizers (PMs) who are receiving bupropion plus a strong CYP3A inhibitor and should be avoided, if possible, in patients who are receiving bupropion plus a moderate CYP3A inhibitor. Concomitant use may increase eliglustat exposure. Eliglustat is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. A strong CYP2D6 inhibitor is predicted to increase eliglustat overall exposure by 8.4-fold and 2.3-fold in extensive and intermediate metabolizers, respectively. Strong CYP2D6s inhibitors alone are not expected to affect eliglustat concentrations in CYP2D6 poor metabolizers (PMs).
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Caution is warranted when cobicistat is administered with bupropion as there is a potential for elevated cobicistat concentrations. Bupropion is a CYP2D6 inhibitor in vitro, while cobicistat is a substrate of CYP2D6.
Ergotamine; Caffeine: (Moderate) Bupropion is associated with a dose-related risk of seizures. Excessive use of psychostimulants, including caffeine, is associated with an increased seizure risk and may increase this risk during the concurrent use of bupropion. Carefully consider a patient's caffeine intake from all sources, including medicines. Monitor for irritability, tremor, increased blood pressure, insomnia and seizures. Many non-prescription medicines and weight loss aids may contain caffeine and patients should read labels carefully. Examples of foods and beverages containing caffeine include coffee, teas, colas, energy drinks, chocolate, and some herbal or dietary supplements. Patients should be advised to limit excessive caffeine intake during

bupropion therapy.
Ethanol: (Major) Advise patients to avoid alcohol consumption while taking bupropion. Bupropion is associated with a dose-related risk of seizures. Alcohol abuse and abrupt discontinuation of alcohol have also been associated with seizures. Neuropsychiatric events and reduced alcohol tolerance have also been described in postmarketing reports.
Ethiodized Oil: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Felbamate: (Major) Bupropion should not be used by patients taking anticonvulsants for seizures because it may decrease the seizure threshold. Bupropion may also interact pharmacokinetically with anticonvulsant drugs that induce hepatic microsomal isoenzyme function.
Fenfluramine: (Major) Do not exceed a maximum dose of fenfluramine 20 mg per day if coadministered with bupropion; for patients also receiving stiripentol plus clobazam, do not exceed a maximum dose of fenfluramine 17 mg per day. Concomitant use may increase fenfluramine plasma concentrations and the risk of adverse reactions. Fenfluramine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Coadministration with another strong CYP2D6 inhibitor increased fenfluramine overall exposure by 81% and decreased norfenfluramine overall exposure by 13%.
fentaNYL: (Moderate) If concomitant use of fentanyl and bupropion is warranted, monitor patients for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Fexinidazole: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of fexinidazole as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose. Bupropion is a sensitive substrate of CYP2B6; fexinidazole is a CYP2B6 inducer.
Fexofenadine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
flavoxATE: (Moderate) Bupropion exhibits moderate anticholinergic effects. Clinicians should keep this in mind when using antimuscarinics and other medications with anticholinergic activity in combination with bupropion.
Flecainide: (Moderate) Monitor for an increase in flecainide-related adverse reactions, including QT prolongation, if coadministration with bupropion is necessary. Flecainide is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Plasma concentrations of flecainide may increase, especially in extensive CYP2D6 metabolizers.

Fludrocortisone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Flunisolide: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
FLUoxetine: (Moderate) Monitor for increased fluoxetine-related adverse effects if coadministered with bupropion. Concomitant use may increase fluoxetine exposure. Fluoxetine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor.
fluPHENAZine: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of fluphenazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of fluphenazine may result in extrapyramidal symptoms, somnolence, or other adverse effects.
Fluticasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Fluticasone; Salmeterol: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Fluticasone; Umeclidinium; Vilanterol: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Fluticasone; Vilanterol: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
fluvoxaMINE: (Moderate) Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Coadministration of bupropion with medications that are metabolized by CYP2D6 should be approached with caution. Many selective serotonin reuptake inhibitors (SSRIs) are CYP2D6 substrates including fluvoxamine. Although clinical evidence of interactions is lacking, plasma concentrations of SSRIs metabolized by CYP2D6 may be increased if bupropion is added. In addition, in

vitro studies suggest that fluvoxamine inhibits the hydroxylation of bupropion.
Formoterol; Mometasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Foscarbidopa; Foslevodopa: (Moderate) Monitor for symptoms of CNS toxicity, such as restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness, if concomitant use of levodopa and bupropion is necessary. Both medications have dopamine agonist effects and use may increase the risk for dopamine-related adverse reactions.
Fosphenytoin: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of fosphenytoin as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose.
Gefitinib: (Moderate) Monitor for an increase in gefitinib-related adverse reactions if coadministration with bupropion is necessary; the risk is increased in CYP2D6 poor metabolizers. Based on in vitro data, gefitinib is metabolized to O-desmethyl gefitinib by CYP2D6 and bupropion is a strong CYP2D6 inhibitor. In healthy CYP2D6 poor metabolizers, the concentration of O-desmethyl gefitinib was not measurable and mean exposure to gefitinib was 2-fold higher compared to extensive metabolizers. The impact of CYP2D6 inhibitors on gefitinib pharmacokinetics has not been evaluated; however, the manufacturer recommends precautions based on exposure in patients with poor CYP2D6 metabolism.
Gepirone: (Moderate) Monitor for serotonin syndrome if concomitant use of gepirone and bupropion is necessary. Both medications affect the serotonergic neurotransmitter system; concomitant use increases the risk for serotonin syndrome.
Glycopyrrolate: (Moderate) Additive anticholinergic effects may be seen when glycopyrrolate is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Glycopyrrolate; Formoterol: (Moderate) Additive anticholinergic effects may be seen when glycopyrrolate is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
guaiFENesin; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
guanFACINE: (Moderate) There is one case report that describes a grand mal seizure that occurred in a child of 10 years of age receiving guanfacine and bupropion concurrently. It is not possible, based on this limited report, to determine if guanfacine was a contributor to the event. Causality has not been established.

Haloperidol: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored. In addition, bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Coadministration of bupropion with medications that are metabolized by the CYP2D6 isoenzyme, such as haloperidol, should be approached with caution. Dosage reductions of haloperidol may be needed. Conversely, if bupropion therapy is discontinued, the antipsychotic dosage may need to be increased in some patients.
Homatropine; HYDROcodone: (Moderate) Additive anticholinergic effects may be seen when homatropine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
(Moderate) Concomitant use of hydrocodone with bupropion may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of bupropion could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If bupropion is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP2D6. Bupropion is a strong inhibitor of CYP2D6.
HYDROcodone: (Moderate) Concomitant use of hydrocodone with bupropion may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of bupropion could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If bupropion is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP2D6. Bupropion is a strong inhibitor of CYP2D6.
HYDROcodone; Ibuprofen: (Moderate) Concomitant use of hydrocodone with bupropion may increase hydrocodone plasma concentrations and prolong opioid adverse reactions, including hypotension, respiratory depression, profound sedation, coma, and death. It is recommended to avoid this combination when hydrocodone is being used

for cough. If coadministration is necessary, monitor patients closely at frequent intervals and consider a dosage reduction of hydrocodone until stable drug effects are achieved. Discontinuation of bupropion could decrease hydrocodone plasma concentrations, decrease opioid efficacy, and potentially lead to a withdrawal syndrome in those with physical dependence to hydrocodone. If bupropion is discontinued, monitor the patient carefully and consider increasing the opioid dosage if appropriate. Hydrocodone is a substrate for CYP2D6. Bupropion is a strong inhibitor of CYP2D6.
Hydrocortisone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
HYDROmorphone: (Moderate) Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.
Hyoscyamine: (Moderate) Additive anticholinergic effects may be seen when hyoscyamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Contraindicated) Due to an increased risk of hypertensive reactions, treatment initiation with bupropion is contraindicated in patients currently receiving intravenous methylene blue. If urgent psychiatric treatment is required, interventions other than bupropion (e.g., alternative medication, hospitalization) should be considered. Conversely, in patients receiving bupropion and requiring urgent treatment with intravenous methylene blue, bupropion should be discontinued immediately and methylene blue therapy initiated only if acceptable alternatives are not available and the potential benefits of methylene blue outweigh the risks. The patient should be monitored for hypertensive reactions for two weeks or until 24 hours after the last dose of methylene blue, whichever comes first. Bupropion may be re-initiated 24 hours after the last dose of methylene blue. It is not known if administration of methylene blue by other routes (e.g., orally, local injection) or in doses less than 1 mg/kg IV can produce a similar outcome. (Moderate) Additive anticholinergic effects may be seen when hyoscyamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Ibuprofen; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Iloperidone: (Major) Reduce the iloperidone dose by one-half if coadministered with

bupropion. If bupropion is discontinued, increase the iloperidone dose to the previous level. Increased iloperidone exposure may occur with concurrent use. Additionally, bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. Iloperidone is a CYP2D6 substrate. Bupropion is a strong inhibitor of CYP2D6. Coadministration of other strong CYP2D6 inhibitors increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by up to 3-fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half.
Imipramine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Indacaterol; Glycopyrrolate: (Moderate) Additive anticholinergic effects may be seen when glycopyrrolate is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Iobenguane I 131: (Major) Discontinue bupropion for at least 5 half-lives before the administration of the dosimetry dose or a therapeutic dose of iobenguane I-131. Do not restart bupropion until at least 7 days after each iobenguane I-131 dose. Drugs that reduce catecholamine uptake or deplete catecholamine stores, such as bupropion, may interfere with iobenguane I-131 uptake into cells and interfere with dosimetry calculations resulting in altered iobenguane I-131 efficacy.
Iodixanol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ioflupane I 123: (Major) Hold bupropion for 8 days, or at least 5 medication half-lives, prior to performing dopamine transporter (DAT) imaging with radiolabeled ioflupane. Bupropion binds to the dopamine transporter which may interfere with striatal tracer binding and increase the risk for a false-positive scan.
Iohexol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.

Iomeprol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopamidol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Iopromide: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ioversol: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Isavuconazonium: (Moderate) Caution and close monitoring are advised when administering isavuconazonium concurrently with buproprion, as decreased buproprion serum concentrations may result. If decreased bupropion efficacy is noted, it may be necessary to increase the dose (not to exceed the maximum recommended dose). Isavuconazole, the active moiety of isavuconazonium, is an inducer of hepatic isoenzyme CYP2B6; bupropion is metabolized by this enzyme.
Isocarboxazid: (Contraindicated) Monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders are contraindicated for use with bupropion or within 14 days of discontinuing treatment with bupropion. Conversely, bupropion should not be initiated within 14 days of stopping an MAOI. There is an increased risk of hypertensive reactions when bupropion is used concurrently with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism, such as MAOIs.
Isosulfan Blue: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents. Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Ivosidenib: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of ivosidenib. A bupropion dose increase may be necessary; do not exceed the maximum recommended dose. Bupropion is a sensitive substrate of CYP2B6; ivosidenib may induce CYP2B6 leading to decreased bupropion concentrations.
Lasmiditan: (Moderate) Serotonin syndrome may occur during coadministration of lasmiditan and bupropion. Inform patients taking this combination of the possible increased risk and monitor for the emergence of serotonin syndrome particularly after a dose increase or the addition of other serotonergic medications to an existing regimen.

Discontinue all serotonergic agents if serotonin syndrome occurs and implement appropriate medical management.
Lemborexant: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of lemborexant as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose for the specific product prescribed. Bupropion is a sensitive substrate of CYP2B6; lemborexant is a weak CYP2B6 inducer.
Levodopa: (Moderate) Monitor for symptoms of CNS toxicity, such as restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness, if concomitant use of levodopa and bupropion is necessary. Both medications have dopamine agonist effects and use may increase the risk for dopamine-related adverse reactions.
Linezolid: (Contraindicated) Due to an increased risk of hypertensive reactions, treatment initiation with bupropion is contraindicated in patients currently receiving linezolid, an antibiotic that is also a non-selective monoamine oxidase (MAO) inhibitor. If urgent psychiatric treatment is required, interventions other than bupropion (e.g., alternative medication, hospitalization) should be considered. Conversely, in patients receiving bupropion and requiring urgent treatment with linezolid, bupropion should be discontinued immediately and linezolid therapy initiated only if acceptable alternatives are not available and the potential benefits of linezolid outweigh the risks. The patient should be monitored for hypertensive reactions for two weeks or until 24 hours after the last dose of linezolid, whichever comes first. Bupropion may be re-initiated 24 hours after the last dose of linezolid.
Lisdexamfetamine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including lisdexamfetamine. Use low initial doses of bupropion and increase the dose gradually.
Lofexidine: (Moderate) Monitor for orthostatic hypotension and bradycardia during concurrent use of lofexidine and bupropion. Coadministration may increase lofexidine exposure. Lofexidine is a CYP2D6 substrate; bupropion is a strong CYP2D6 inhibitor. Coadministration with a strong CYP2D6 inhibitor increased the lofexidine AUC by 28%.
Lopinavir; Ritonavir: (Moderate) Concurrent administration of bupropion with ritonavir results in decreased concentrations of bupropion and its active metabolite. According to the manufacturers of bupropion, increased doses of bupropion may be necessary during concurrent therapy; however, the maximum recommended dose of bupropion should not be exceeded. Closely monitor bupropion efficacy if these drugs are given together. Ritonavir induces CYP2B6, which is responsible for bupropion's metabolism. In one study, ritonavir 100 mg twice daily reduced the AUC and Cmax of bupropion by 22% and 21%, respectively. In addition, exposure to the active metabolite of bupropion (hydroxybupropion) was decreased by 23%. When given with ritonavir 600 mg twice daily, the AUC and Cmax of bupropion decreased by 66% and 63% respectively and exposure to hydroxybupropion decreased by 78%.

Loratadine; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Loxapine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
Lumacaftor; Ivacaftor: (Moderate) Lumacaftor; ivacaftor may reduce the efficacy of bupropion by decreasing its systemic exposure. If used together, monitor patients closely for loss of bupropion efficacy; a bupropion dosage adjustment may be required to obtain the desired therapeutic effect. Do not exceed the maximum recommended dose. Bupropion is a substrate of CYP2B6; in vitro data suggest that lumacaftor may induce this enzyme.
Lumacaftor; Ivacaftor: (Moderate) Lumacaftor; ivacaftor may reduce the efficacy of bupropion by decreasing its systemic exposure. If used together, monitor patients closely for loss of bupropion efficacy; a bupropion dosage adjustment may be required to obtain the desired therapeutic effect. Do not exceed the maximum recommended dose. Bupropion is a substrate of CYP2B6; in vitro data suggest that lumacaftor may induce this enzyme.
Lurasidone: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
Maprotiline: (Major) Concurrent administration of maprotiline with bupropion should be undertaken only with extreme caution due to the potential for increased risk of seizures from the lowering of seizure threshold. In addition, bupropion inhibits the hepatic isozyme CYP2D6 and thus may reduce the clearance of maprotiline leading to a potential for increased Cmax, AUC and half-life. Maprotiline appears to be metabolized via CYP2D6. Low initial dosing and gradual dose increases of both drugs should be employed. If bupropion is added to a regimen of a patient already receiving maprotiline, the need to reduce the maprotiline dosage should be considered.
Meperidine: (Moderate) Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.
Methadone: (Moderate) Consider a reduced dose of methadone with frequent monitoring for respiratory depression and sedation if concurrent use of bupropion is necessary. If bupropion is discontinued, methadone plasma concentrations can

decrease resulting in reduced efficacy and potential withdrawal syndrome in a patient who has developed physical dependence to methadone. Methadone is a substrate of CYP3A4, CYP2B6, CYP2C19, CYP2C9, and CYP2D6; bupropion is a strong CYP2D6 inhibitor. Concomitant use with bupropion can increase methadone exposure resulting in increased or prolonged opioid effects including fatal respiratory depression, particularly when an inhibitor is added to a stable dose of methadone.
Methamphetamine: (Major) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as methamphetamine. If used together, use low initial doses of bupropion and increase the dose gradually.
Methenamine; Sodium Acid Phosphate; Methylene Blue; Hyoscyamine: (Contraindicated) Due to an increased risk of hypertensive reactions, treatment initiation with bupropion is contraindicated in patients currently receiving intravenous methylene blue. If urgent psychiatric treatment is required, interventions other than bupropion (e.g., alternative medication, hospitalization) should be considered. Conversely, in patients receiving bupropion and requiring urgent treatment with intravenous methylene blue, bupropion should be discontinued immediately and methylene blue therapy initiated only if acceptable alternatives are not available and the potential benefits of methylene blue outweigh the risks. The patient should be monitored for hypertensive reactions for two weeks or until 24 hours after the last dose of methylene blue, whichever comes first. Bupropion may be re-initiated 24 hours after the last dose of methylene blue. It is not known if administration of methylene blue by other routes (e.g., orally, local injection) or in doses less than 1 mg/kg IV can produce a similar outcome. (Moderate) Additive anticholinergic effects may be seen when hyoscyamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Methohexital: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Methscopolamine: (Moderate) Additive anticholinergic effects may be seen when methscopolamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Methylene Blue: (Contraindicated) Due to an increased risk of hypertensive reactions, treatment initiation with bupropion is contraindicated in patients currently receiving

intravenous methylene blue. If urgent psychiatric treatment is required, interventions other than bupropion (e.g., alternative medication, hospitalization) should be considered. Conversely, in patients receiving bupropion and requiring urgent treatment with intravenous methylene blue, bupropion should be discontinued immediately and methylene blue therapy initiated only if acceptable alternatives are not available and the potential benefits of methylene blue outweigh the risks. The patient should be monitored for hypertensive reactions for two weeks or until 24 hours after the last dose of methylene blue, whichever comes first. Bupropion may be re-initiated 24 hours after the last dose of methylene blue. It is not known if administration of methylene blue by other routes (e.g., orally, local injection) or in doses less than 1 mg/kg IV can produce a similar outcome.
Methylphenidate Derivatives: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including methylphenidate. Use low initial doses of bupropion and increase the dose gradually.
Methylphenidate: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including methylphenidate. Use low initial doses of bupropion and increase the dose gradually.
methylPREDNISolone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Metoclopramide: (Major) When metoclopramide is used with a potent CYP2D6 inhibitor for the treatment of gastroesophageal reflux (GERD), dosage reductions of oral metoclopramide are required, with maximum oral dosage not to exceed 30 mg/day (e.g., 5 mg 4 times daily or 10 mg 3 times daily). There is a known increase in metoclopramide exposure and an increased risk for extrapyramidal adverse reactions. Metoclopramide is a substrate of CYP2D6 and bupropion is a strong CYP2D6 inhibitor. The manufacturer recommends avoidance of bupropion when oral metoclopramide is used in patients with diabetic gastroparesis. Healthy patients given 20 mg of metoclopramide and a potent CYP2D6 inhibitor for 8 days had a 40% and 90% increase in metoclopramide Cmax and AUC, respectively, compared to patients who received metoclopramide alone.
Metoprolol: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with bupropion. Concomitant use may increase metoprolol serum concentrations which would decrease the cardioselectivity of metoprolol. Metoprolol is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Coadministration with strong CYP2D6 inhibitors has been shown to double metoprolol concentrations.
Metoprolol; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor for metoprolol-related adverse reactions, including bradycardia and hypotension, during coadministration with

bupropion. Concomitant use may increase metoprolol serum concentrations which would decrease the cardioselectivity of metoprolol. Metoprolol is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Coadministration with strong CYP2D6 inhibitors has been shown to double metoprolol concentrations.
Mexiletine: (Major) Coadministration of bupropion and mexiletine can increase the exposure of mexiletine. If used together, it may be necessary to decrease the dose of mexiletine and slowly titrate to effect. Mexiletine is primarily metabolized via CYP2D6 and bupropion and its metabolites are inhibitors of CYP2D6.
Midazolam: (Moderate) Bupropion is contraindicated in patients undergoing abrupt withdrawal of benzodiazepines since the risk of seizures associated with bupropion may be increased. Excessive use of benzodiazepines is associated with an increased seizure risk; seizures may be more likely to occur in these patients during concurrent use of bupropion.
Midostaurin: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of midostaurin as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose. Bupropion is a sensitive substrate of CYP2B6; midostaurin is a moderate CYP2B6 inducer.
miFEPRIStone: (Moderate) Monitor for an increase in bupropion-related adverse reactions during coadministration of mifepristone as concurrent use may increase bupropion exposure. A bupropion dose adjustment may be necessary. Bupropion is a sensitive substrate of CYP2B6; mifepristone is a moderate CYP2B6 inhibitor.
Mitapivat: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of mitapivat as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose. Bupropion is a sensitive substrate of CYP2B6; mitapivat is a weak CYP2B6 inducer.
Modafinil: (Major) Bupropion is associated with a dose-related risk of seizures. It is unclear whether modafinil lowers the seizure threshold. Seizures have occurred during post-marketing use of modafinil, although the frequency is unknown.
Molindone: (Major) Drugs which may lower the seizure threshold, such as molindone, should be used with great caution or avoided in patients taking bupropion. The manufacturer recommends low initial dosing and slow dosage titration of bupropion if this combination must be used concurrently; the patient should be closely monitored.
Mometasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Monoamine oxidase inhibitors: (Contraindicated) Monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders are contraindicated for use with bupropion or within 14 days of discontinuing treatment with bupropion. Conversely, bupropion

should not be initiated within 14 days of stopping an MAOI. There is an increased risk of hypertensive reactions when bupropion is used concurrently with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism, such as MAOIs.
Morphine: (Moderate) Monitor for seizure activity during concomitant bupropion and morphine use. Bupropion is associated with a dose-related seizure risk and excessive opioid use also increases seizure risk.
Naproxen; Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Nebivolol: (Moderate) Monitor for increased toxicity as well as increased therapeutic effect of nebivolol if coadministered with bupropion; adjust the nebivolol dose according to blood pressure response. Concomitant use may increase the exposure of nebivolol. Nebivolol is a CYP2D6 substrate and bupropion is a moderate CYP2D6 inhibitor.
Nelfinavir: (Minor) In vitro studies suggest that nelfinavir inhibits the hydroxylation of bupropion. The clinical significance of this finding is unknown.
Neostigmine; Glycopyrrolate: (Moderate) Additive anticholinergic effects may be seen when glycopyrrolate is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Nicotine: (Moderate) Monitor blood pressure during concomitant bupropion and nicotine use. Clinical trial data suggest a higher incidence of treatment-emergent hypertension during concomitant use.
Nirmatrelvir; Ritonavir: (Moderate) Concurrent administration of bupropion with ritonavir results in decreased concentrations of bupropion and its active metabolite. According to the manufacturers of bupropion, increased doses of bupropion may be necessary during concurrent therapy; however, the maximum recommended dose of bupropion should not be exceeded. Closely monitor bupropion efficacy if these drugs are given together. Ritonavir induces CYP2B6, which is responsible for bupropion's metabolism. In one study, ritonavir 100 mg twice daily reduced the AUC and Cmax of bupropion by 22% and 21%, respectively. In addition, exposure to the active metabolite of bupropion (hydroxybupropion) was decreased by 23%. When given with ritonavir 600 mg twice daily, the AUC and Cmax of bupropion decreased by 66% and 63% respectively and exposure to hydroxybupropion decreased by 78%.
Nitroglycerin: (Minor) Nitroglycerin can cause hypotension. This action may be additive with other agents that can cause hypotension such as antidepressants. Patients should be monitored more closely for hypotension if nitroglycerin is used concurrently with antidepressants.
Non-Ionic Contrast Media: (Major) Use of medications that lower the seizure threshold should be carefully evaluated when considering intrathecal radiopaque contrast agents.

Bupropion should be discontinued at least 48 hours before myelography and should not be resumed for at least 24 hours postprocedure.
Nortriptyline: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
OLANZapine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
OLANZapine; FLUoxetine: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored. (Moderate) Monitor for increased fluoxetine-related adverse effects if coadministered with bupropion. Concomitant use may increase fluoxetine exposure. Fluoxetine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor.
OLANZapine; Samidorphan: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
Oliceridine: (Moderate) Monitor patients closely for respiratory depression and sedation at frequent intervals and base subsequent doses on the patient's severity of pain and response to treatment if concomitant administration of oliceridine and bupropion is necessary; less frequent dosing of oliceridine may be required. Concomitant use of oliceridine and bupropion may increase the plasma concentration of oliceridine, resulting in increased or prolonged opioid effects. If bupropion is discontinued, consider increasing the oliceridine dose until stable drug effects are achieved and monitor for evidence of opioid withdrawal. Oliceridine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Also monitor patients for the emergence of serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs. The concomitant use of opioids with other drugs that affect

the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Olopatadine; Mometasone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
OXcarbazepine: (Moderate) Bupropion should not be used by patients with a preexisting seizure disorder because it may lower the seizure threshold.
oxyMORphone: (Moderate) Excessive use of opioid agonists (e.g., opiate addiction) is associated with an increased seizure risk; seizures may be more likely to occur during concurrent use of bupropion in these patients since bupropion is associated with a dose-related risk of seizures.
Paliperidone: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as paliperidone. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
PARoxetine: (Moderate) Monitor for an increase in paroxetine-related adverse reactions, including serotonin syndrome, if concomitant use with bupropion is necessary. Concomitant use may increase paroxetine exposure. Paroxetine is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor.
Pentazocine; Naloxone: (Moderate) Plasma concentrations of opiate agents metabolized by CYP2D6, such as pentazocine, may be increased if bupropion, an inhibitor of the CYP2D6 isoenzyme, is added. Dosage reductions of pentazocine may be needed. Conversely, if bupropion therapy is discontinued, dosages of pentazocine may need to be adjusted upward in some patients.
PENTobarbital: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Perphenazine: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of perphenazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of perphenazine may result in extrapyramidal symptoms, somnolence, or other adverse effects.

Perphenazine; Amitriptyline: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of perphenazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of perphenazine may result in extrapyramidal symptoms, somnolence, or other adverse effects. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Phendimetrazine: (Major) Bupropion is associated with a dose-related risk of seizures. Excessive use of phendimetrazine is associated with an increased seizure risk; seizures may be more likely to occur in these patients during concurrent use of bupropion. Patients should be closely monitored if these combinations are necessary.
Phenelzine: (Contraindicated) Monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders are contraindicated for use with bupropion or within 14 days of discontinuing treatment with bupropion. Conversely, bupropion should not be initiated within 14 days of stopping an MAOI. There is an increased risk of hypertensive reactions when bupropion is used concurrently with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism, such as MAOIs.
PHENobarbital: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
PHENobarbital; Hyoscyamine; Atropine; Scopolamine: (Moderate) Additive anticholinergic effects may be seen when hyoscyamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. (Moderate) Additive anticholinergic effects may be seen when scopolamine is used concomitantly with bupropion. Additive drowsiness may

occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
(Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. (Moderate) The anticholinergic effects of atropine may be enhanced when combined with other drugs with moderate to significant anticholinergic effects including bupropion. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation. Additive drowsiness may also occur.
Phentermine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including phentermine. Use low initial doses of bupropion and increase the dose gradually.
Phentermine; Topiramate: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including phentermine. Use low initial doses of bupropion and increase the dose gradually.
Phenytoin: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of phenytoin as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose.
Pimozide: (Contraindicated) Coadministration of pimozide and bupropion is contraindicated due to the potential for increased pimozide exposure. Elevated concentrations of pimozide can lead to QT prolongation, ventricular arrhythmias, and sudden death. The risk of seizure may also be increased as both drugs lower the seizure threshold. Bupropion is a strong CYP2D6 inhibitor; pimozide is a CYP2D6 substrate. Coadministration of pimozide with another strong CYP2D6 inhibitor increased the pimozide AUC by 151%.
Pitolisant: (Major) A pitolisant dosage reduction may be required during concomitant bupropion use. For patients on a stable dose of pitolisant, reduce the pitolisant dosage by half. For patients starting pitolisant, reduce the maximum recommended dosage by half to 17.8 mg once daily for adults and patients 6 years and older weighing 40 kg or more or 8.9 mg once daily for patients 6 years and older weighing less than 40 kg. Concomitant use may increase pitolisant exposure and the risk for pitolisant-related adverse effects. Pitolisant is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased pitolisant

overall exposure by 2.2-fold.
prednisoLONE: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
predniSONE: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Primidone: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Prochlorperazine: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of prochlorperazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of prochlorperazine may result in extrapyramidal symptoms, somnolence, or other adverse effects.
Promethazine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as promethazine. Use low initial doses of bupropion and increase the dose gradually.
Promethazine; Dextromethorphan: (Moderate) Monitor for dextromethorphan-related side effects, such as dizziness or drowsiness, if concomitant use of bupropion is necessary. Concomitant use may increase dextromethorphan exposure and side effects. Dextromethorphan is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with another strong CYP2D6 inhibitor increased dextromethorphan overall exposure by 2.69-fold. (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as promethazine. Use low initial doses of bupropion and increase the dose gradually.
Promethazine; Phenylephrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as promethazine. Use low initial doses of bupropion and increase the dose gradually.
Propafenone: (Moderate) Monitor for increased propafenone toxicity if coadministered with bupropion; concurrent use may increase propafenone exposure and therefore

increase the risk of proarrhythmias. Avoid simultaneous use of propafenone and bupropion with a CYP3A4 inhibitor. Propafenone is a CYP3A4 and CYP2D6 substrate; bupropion is a strong CYP2D6 inhibitor.
Propantheline: (Moderate) Additive anticholinergic effects may be seen when propantheline is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Propranolol: (Minor) Monitor for an increased incidence of propranolol-related adverse effects if bupropion and propranolol are used concomitantly. Coadministration of bupropion and propranolol may result in increased plasma concentrations of propranolol. Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Propranolol is a CYP2D6 substrate.
Protriptyline: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Pseudoephedrine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Pseudoephedrine; Triprolidine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as pseudoephedrine. Use low initial doses of bupropion and increase the dose gradually.
Ranolazine: (Moderate) Bupropion inhibits CYP2D6. Coadministration of bupropion with medications that are metabolized by CYP2D6, like ranolazine, may result in increased ranolazine plasma concentrations if bupropion is added.
Rasagiline: (Contraindicated) Monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders are contraindicated for use with bupropion or within 14 days of discontinuing treatment with bupropion. Conversely, bupropion should not be initiated within 14 days of stopping an MAOI. There is an increased risk of hypertensive reactions when bupropion is used concurrently with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism, such as MAOIs. The manufacturer of rasagiline advises against concurrent use with any antidepressant.
rifAMPin: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function such as rifampin. Pharmacokinetic studies describe patients who developed subtherapeutic bupropion serum concentrations when enzyme-inducing

agents were added. In healthy volunteers, coadministration of bupropion with rifampin reduced the mean AUC of bupropion by 3-fold and the mean half-life from 15.9 hours to 8.2 hours.
risperiDONE: (Moderate) Monitor for an increase in risperidone-related adverse effects if concomitant use with bupropion is necessary and reduce risperidone dosage as appropriate based on response. For patients receiving long-acting risperidone dosage forms, an anticipatory dosage decrease may be considered prior to initiation of bupropion. Concomitant use may increase risperidone exposure. Additionally, bupropion is associated with a dose-related increase in seizures; antipsychotics may increase this risk. Risperidone is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant use with other strong CYP2D6 inhibitors increased risperidone overall exposure by 2.5- to 9-fold.
Ritonavir: (Moderate) Concurrent administration of bupropion with ritonavir results in decreased concentrations of bupropion and its active metabolite. According to the manufacturers of bupropion, increased doses of bupropion may be necessary during concurrent therapy; however, the maximum recommended dose of bupropion should not be exceeded. Closely monitor bupropion efficacy if these drugs are given together. Ritonavir induces CYP2B6, which is responsible for bupropion's metabolism. In one study, ritonavir 100 mg twice daily reduced the AUC and Cmax of bupropion by 22% and 21%, respectively. In addition, exposure to the active metabolite of bupropion (hydroxybupropion) was decreased by 23%. When given with ritonavir 600 mg twice daily, the AUC and Cmax of bupropion decreased by 66% and 63% respectively and exposure to hydroxybupropion decreased by 78%.
Scopolamine: (Moderate) Additive anticholinergic effects may be seen when scopolamine is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Secobarbital: (Moderate) Bupropion may interact with drugs that induce hepatic microsomal isoenzyme function via CYP2B6 such as the barbiturates. While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded. Advise patients that until they are reasonably certain that the combination does not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery.
Selegiline: (Contraindicated) The manufacturer of bupropion contraindicates use with monoamine oxidase inhibitors (MAOIs) due to the risk of hypertensive crisis. At least 14 days should elapse between discontinuation of selegiline and initiation of treatment with bupropion. After stopping treatment with bupropion, a time period equal to 4 to 5 half-lives of bupropion or any active metabolite should elapse before starting therapy

with selegiline.
Serdexmethylphenidate; Dexmethylphenidate: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as stimulants including methylphenidate. Use low initial doses of bupropion and increase the dose gradually.
Sertraline: (Minor) Concomitant use of bupropion and sertraline may theoretically increase the risk for sertraline-related adverse effects in some patients. Adjunctive therapy with bupropion plus a selective serotonin reuptake inhibitor (SSRI), like sertraline, is typically associated with improved clinical outcomes, especially in patients with a partial response to monotherapy. In some patients, an increase in exposure to sertraline or its metabolites may occur. Sertraline is metabolized by a variety of CYP enzymes including CYP2D6; bupropion is a strong CYP2D6 inhibitor. The concomitant use of strong CYP2D6 inhibitors, like bupropion, is not expected to have a meaningful effect on concentrations of sertraline or its metabolites in most patients.
Sodium Oxybate: (Major) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as sodium oxybate. The risk of seizures with bupropion is dose related and is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment If used together, use low initial doses of bupropion and increase the dose gradually.
Sodium Phenylbutyrate; Taurursodiol: (Moderate) Monitor for decreased efficacy and/or increased bupropion-related adverse effects if concomitant use of taurursodiol is necessary. A bupropion dose adjustment may be necessary. Concomitant use may alter bupropion exposure. Bupropion is a sensitive substrate of CYP2B6; taurursodiol is a weak CYP2B6 inhibitor and inducer. The net effect on bupropion exposure is unknown.
Solriamfetol: (Moderate) Monitor for dopamine-mediated effects including nausea, vomiting, dizziness, tremor, and changes in moods or behaviors if solriamfetol, a central dopamine and norepinephrine reuptake inhibitor, is administered with other dopaminergic drugs, such as bupropion. Caution is recommended since this combination has not been evaluated.
Sparsentan: (Moderate) Monitor for loss of efficacy of bupropion during coadministration of sparsentan as concurrent use may decrease bupropion exposure. A bupropion dose adjustment may be necessary; do not exceed maximum dose. Bupropion is a sensitive substrate of CYP2B6; sparsentan is a weak CYP2B6 inducer. Concomitant use decreased bupropion overall exposure by 33%.
Stiripentol: (Moderate) Consider a dose adjustment of bupropion when coadministered with stiripentol. Coadministration may alter plasma concentrations of bupropion resulting in an increased risk of adverse reactions and/or decreased efficacy. Bupropion is a sensitive CYP2B6 substrate. In vitro data predicts inhibition or induction of CYP2B6 by stiripentol potentially resulting in clinically significant interactions.

Tamoxifen: (Moderate) Monitor for decreased efficacy of tamoxifen if coadministration with bupropion is necessary. Tamoxifen is metabolized by CYP2D6 to endoxifen and 4-hydroxytamoxifen, both of which are minor metabolites but have 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent cell proliferation than tamoxifen. Bupropion is a strong CYP2D6 inhibitor. In one study, the mean steady-state endoxifen plasma concentration was significantly reduced in patients taking CYP2D6 inhibitors compared to those not taking concomitant CYP2D6 inhibitors. In another study, the mean steady-state plasma concentration of endoxifen in CYP2D6 normal metabolizers who were not receiving CYP2D6 inhibitors were 3.6-fold higher compared to normal metabolizers who were receiving strong CYP2D6 inhibitors; plasma levels in CYP2D6 normal metabolizers receiving strong CYP2D6 inhibitors were similar to levels observed in CYP2D6 poor metabolizers taking no CYP2D6 inhibitors. Some studies have shown that the efficacy of tamoxifen may be reduced when concomitant drugs decrease the levels of potent active metabolites; however, others have failed to demonstrate such an effect. The clinical significance is not well established.
Tamsulosin: (Moderate) Use caution if coadministration of bupropion with tamsulosin is necessary, especially at a tamsulosin dose higher than 0.4 mg, as the systemic exposure of tamsulosin may be increased resulting in increased treatment-related adverse reactions including hypotension, dizziness, and vertigo. Tamsulosin is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor. Concomitant treatment with another strong CYP2D6 inhibitor increased the Cmax and AUC of tamsulosin by a factor of 1.3 and 1.6, respectively.
Theophylline, Aminophylline: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as aminophylline. The manufacturer recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored. In addition, when bupropion is used for smoking cessation, it should be noted that cessation of smoking may result in elevated serum concentrations of some drugs that are hepatically metabolized, such as theophylline or aminophylline, due to lowered induction of hepatic oxidative microsomal enzymes (tobacco smoke induces hepatic enzymes). Downward dosage adjustments of such drugs and more frequent monitoring may be required during smoking cessation. (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as theophylline. The manufacturer recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored. In addition, when bupropion is used for smoking cessation, it should be noted that cessation of smoking may result in elevated serum concentrations of some drugs that are hepatically metabolized, such as theophylline or aminophylline, due to

lowered induction of hepatic oxidative microsomal enzymes (tobacco smoke induces hepatic enzymes). Downward dosage adjustments of such drugs and more frequent monitoring may be required during smoking cessation.
Thioridazine: (Contraindicated) Bupropion is a strong inhibitor of CYP2D6 and the use of thioridazine with CYP2D6 inhibitors is contraindicated due to the possible risk of QT prolongation and subsequent arrhythmias resulting from elevated serum concentrations of thioridazine. In addition, bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines, such as thioridazine, on lowering the seizure threshold.
Thiotepa: (Moderate) The concomitant use of thiotepa and bupropion may increase the exposure of bupropion but decrease hydroxybupropion exposure; however, the clinical relevance of this interaction is unknown. Dosage adjustment of bupropion may be necessary based on clinical response. Thiotepa is a CYP2B6 inhibitor in vitro; bupropion is a sensitive substrate of CYP2B6 in vitro.
Thiothixene: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.
Timolol: (Minor) Monitor for an increased incidence of timolol-related adverse effects if bupropion and timolol are used concomitantly. Coadministration of bupropion and timolol may result in increased plasma concentrations of timolol. Bupropion and hydroxybupropion, the major active metabolite, are inhibitors of CYP2D6 in vitro. Timolol is a CYP2D6 substrate.
Tolterodine: (Moderate) Bupropion exhibits moderate anticholinergic effects. Clinicians should keep this in mind when using antimuscarinics and other medications with anticholinergic activity in combination with bupropion.
traMADol: (Moderate) Monitor for reduced efficacy of tramadol, signs of opioid withdrawal, seizures, or serotonin syndrome if coadministration with bupropion is necessary. If bupropion is discontinued, consider a dose reduction of tramadol and frequently monitor for signs of respiratory depression and sedation. Tramadol is a CYP2D6 substrate and bupropion is a CYP2D6 inhibitor. Concomitant use of tramadol with CYP2D6 inhibitors can increase the plasma concentration of tramadol and decrease the plasma concentration of the active metabolite M1. Since M1 is a more potent mu-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who have developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.

Tramadol; Acetaminophen: (Moderate) Monitor for reduced efficacy of tramadol, signs of opioid withdrawal, seizures, or serotonin syndrome if coadministration with bupropion is necessary. If bupropion is discontinued, consider a dose reduction of tramadol and frequently monitor for signs of respiratory depression and sedation. Tramadol is a CYP2D6 substrate and bupropion is a CYP2D6 inhibitor. Concomitant use of tramadol with CYP2D6 inhibitors can increase the plasma concentration of tramadol and decrease the plasma concentration of the active metabolite M1. Since M1 is a more potent mu-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who have developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome. Discontinue all serotonergic agents and initiate symptomatic treatment if serotonin syndrome occurs.
Tranylcypromine: (Contraindicated) Monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders are contraindicated for use with bupropion or within 14 days of discontinuing treatment with bupropion. Conversely, bupropion should not be initiated within 14 days of stopping an MAOI. There is an increased risk of hypertensive reactions when bupropion is used concurrently with other drugs that inhibit the reuptake of dopamine or norepinephrine or inhibit their metabolism, such as MAOIs.
Triamcinolone: (Moderate) Monitor for seizure activity during concomitant bupropion and corticosteroid use. Bupropion is associated with a dose-related seizure risk; concomitant use of other medications that lower the seizure threshold, such as systemic corticosteroids, increases the seizure risk.
Triazolam: (Moderate) Bupropion is contraindicated in patients undergoing abrupt withdrawal of benzodiazepines since the risk of seizures associated with bupropion may be increased. Excessive use of a benzodiazepine is associated with an increased seizure risk upon discontinuation of the drug; seizures may be more likely to occur in these patients during concurrent use of bupropion.
Tricyclic antidepressants: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Trifluoperazine: (Major) Bupropion is associated with a dose-related risk of seizures and may have an additive effect with phenothiazines on lowering the seizure threshold. Low

initial dosing and slow titration is recommended if this combination must be used. In addition, bupropion is a strong inhibitor of CYP2D6. Dosage reductions of trifluoperazine, a CYP2D6 substrate, may be needed during coadministration with bupropion. Increased serum concentrations of trifluoperazine may result in extrapyramidal symptoms, somnolence, or other adverse effects.
Trihexyphenidyl: (Moderate) Additive anticholinergic effects may be seen when trihexyphenidyl is used concomitantly with bupropion. Additive drowsiness may occur. Clinicians should note that antimuscarinic effects might be seen not only on GI smooth muscle, but also on bladder function, the eye, and temperature regulation.
Trimipramine: (Moderate) Use extreme caution when coadministering bupropion with other drugs that lower the seizure threshold, such as tricyclic antidepressants. Use low initial doses of bupropion and increase the dose gradually. Monitor patients for an increase in tricyclic antidepressant-related adverse reactions and signs and symptoms of serotonin syndrome during concomitant use, particularly during treatment initiation and dosage increases; a dose reduction of the tricyclic antidepressant may be necessary. If serotonin syndrome occurs, consider discontinuation of therapy. The concomitant use of serotonergic drugs increases the risk of serotonin syndrome. Tricyclic antidepressants are CYP2D6 substrates and bupropion is a CYP2D6 inhibitor.
Trospium: (Moderate) Depending on the specific agent, additive anticholinergic effects may be seen when drugs with antimuscarinic properties like trospium and bupropion are used concomitantly. Clinicians should note that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function and temperature regulation. While CNS-related side effects such as drowsiness and blurred vision are not typically noted with trospium, they may occur in some patients.
Valproic Acid, Divalproex Sodium: (Moderate) Bupropion should not be used by patients with a preexisting seizure disorder because it may lower the seizure threshold. Use with caution when valproic acid and its derivatives (valproate, divalproex) are used for other purposes, as additive CNS reactions may be possible. Pharmacokinetic interactions have not been noted.
Vortioxetine: (Major) The primary isoenzyme involved in the metabolim of vortioxetine is CYP2D6; therefore, the manufacturer recommends a reduction in the vortioxetine dose by one-half during co-administration with strong inhibitors of CYP2D6 such as bupropion. The vortioxetine dose should be increased to the original level when the CYP2D6 inhibitor is discontinued.
Warfarin: (Moderate) When bupropion is used for smoking cessation, be aware that changes in the INR may occur in patients previously stabilized on warfarin as tobacco smoking is reduced or halted, as smoking affects CYP1A2, one of the enzymes involved in warfarin metabolism. Physiological changes resulting from smoking cessation, with or without treatment with bupropion, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g.,warfarin) for which dosage adjustment may be

necessary. A case report of potential interaction with warfarin and bupropion used for depression has been reported; when bupropion was abruptly halted in the patient prior to surgery, the patient's INR increased to 8.0. The authors could not discern a probable mechanism for the potential interaction, but the patient was also reducing his daily tobacco smoking status, Patients who are receiving warfarin with bupropion should be carefully monitored if the patient is also altering their smoking status.
Xanomeline; Trospium: (Moderate) Depending on the specific agent, additive anticholinergic effects may be seen when drugs with antimuscarinic properties like trospium and bupropion are used concomitantly. Clinicians should note that additive antimuscarinic effects may be seen not only on GI smooth muscle, but also on bladder function and temperature regulation. While CNS-related side effects such as drowsiness and blurred vision are not typically noted with trospium, they may occur in some patients. (Moderate) Monitor for an increase in xanomeline-related adverse effects if concomitant use with bupropion is necessary. Concomitant use may increase xanomeline exposure. Xanomeline is a CYP2D6 substrate and bupropion is a strong CYP2D6 inhibitor.
Ziprasidone: (Major) Bupropion is associated with a dose-related risk of seizures. Extreme caution is recommended during concurrent use of other drugs that may lower the seizure threshold such as antipsychotics. The manufacturer of bupropion recommends low initial dosing and slow dosage titration if this combination must be used; the patient should be closely monitored.

Adverse Reaction

seizures

Bupropion exhibits a greater potential for causing seizures than other antidepressants; the incidence of seizures with bupropion exceeds that of other commercially available antidepressants by up to 4-fold. The incidence of seizures occurring with bupropion is dose-dependent. Seizures occur in roughly 0.1% of patients receiving up to 300 mg/day (sustained-release) and 0.4% of patients receiving up to 450 mg/day (immediate-release) of bupropion. According to the manufacturer, the incidence of seizures in patients taking Wellbutrin XL as a single dose of 450 mg is 0.4%. Although seizure incidence has not been evaluated in clinical trials of the extended-release formulation of bupropion, its bioequivalence with the immediate-release and sustained-release formulations suggests that the risk may be similar to that encountered with use of these products. The incidence of seizures rises disproportionately at dosages greater than 450 mg/day (immediate-release). In patients receiving a 600 mg/day immediate-release regimen of bupropion, the risk of seizures was estimated to be 10-fold that of patients administered the 450 mg maximum daily recommended dose. The incidence of seizures during use of

bupropion hydrobromide (Aplenzin) has not been formally evaluated by the manufacturer. To limit the risk of seizures, recommended single or maximum daily dosages of any dosage form of bupropion should not be exceeded. Some patients may be more at risk of experiencing seizures with bupropion therapy. The use or withdrawal of some medication regimens, including ethanol, may lower seizure threshold; these should be utilized cautiously with bupropion. When possible, concomitant use of these medications with bupropion should be avoided.

aphasia, aseptic meningitis, ataxia, coma, dizziness, drowsiness, dysarthria, EEG changes, headache, hypoesthesia, insomnia, lethargy, migraine, neuropathic pain, paresthesias, restlessness, tremor, vertigo

During clinical trials of immediate-release or extended-release bupropion formulations for depression and mood disorders, the following centrally-mediated effects occurred more frequently with bupropion than with placebo: insomnia (11% to 31%), dizziness (6% to 11%), tremor (2% to 21.1%), drowsiness (2% to 3%), sedation or lethargy (19.8%), cutaneous temperature disturbance (1.9%), headache (25% to 34%), migraine (1% to 25.7%), impaired sleep quality (4%), paresthesias (1% to 2%), CNS stimulation or restlessness (1% to 2%), and feeling jittery (3%). In a comparative smoking cessation treatment trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy or Zyban/NTS combination, the following central nervous system (CNS) effects and incidences were reported: insomnia (40%, 28%, 45%) and nervousness (1%, less than 1%, 2%). Other CNS effects reported in 0.1% to 1% of bupropion-treated subjects have included ataxia/incoordination, vertigo, dysarthria, abnormal coordination, CNS stimulation, hypoesthesia, and paresthesias. Rarely reported effects (less than 0.1%) included EEG changes, abnormal neurological exam, impaired attention, and aphasia. Also observed were coma, neuralgia (neuropathic pain), neuropathy, and restlessness. Aseptic meningitis has been reported during postmarketing surveillance. Some CNS symptoms may be dose-related and may respond to dosage reduction. To limit insomnia, do not give doses close to bedtime. In some cases insomnia may require treatment with sedative/hypnotic therapy. In roughly 2% of bupropion recipients, such CNS symptoms will necessitate drug discontinuation.

mania

All effective antidepressants can precipitate mania in predisposed individuals suffering from bipolar disorder. Mania and hypomania have been reported in 1% or more of bupropion recipients during clinical trials. Hypomania was reported rarely (less than 0.1%) during other pre-marketing evaluations. If mania occurs, bupropion should be held and appropriate therapy to treat the manic symptoms should be initiated.

abnormal dreams, agitation, amnesia, anxiety, confusion, delirium, dysphoria, emotional lability, hallucinations, hostility, irritability, memory impairment, paranoia, psychosis

Psychiatric effects reported more frequently with immediate-release or extended-release bupropion formulations than placebo during clinical trials included agitation (2% to 31.9%), anxiety (3.1% to 8%), memory impairment (less than 0.5 and up to 3%), confusion (8.4%), delusions (1.2%), impaired concentration (3.1% to 9%), hostility (5.6%), irritability (2% to 3%), thinking abnormality (1%), and abnormal dreams (3% to 5%). These reactions may happen in patients treated for major depressive disorder (MDD) or in those who use bupropion for smoking cessation. In a comparative trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, the following psychiatric effects and incidences were reported: dysphoria (less than 1%, 1%, 2%, 1%), anxiety (8%, 6%, 9%, 6%), impaired concentration (9%, 3%, 9%, 4%), and abnormal dreams (5%, 18%, 13%, 3%). During other pre-marketing or postmarketing use, hallucinations and agitation occurred in 1% or more of patients. Memory impairment, depersonalization, psychosis, confusion, dysphoria, emotional lability, hostility, paranoia, formal thought disorder (unspecified), and frigidity were reported in 0.1 to 1% of patients. Amnesia and derealization occurred rarely (less than 0.1%). Also observed were aggression, delirium, delusions. Aggression, paranoia, and abnormal dreams have been reported during postmarketing use.

akathisia, depression, suicidal ideation

Depressive symptoms have been reported in smoking cessation studies as well as psychiatric studies with bupropion. During clinical trials for major depressive disorder, akathisia (psychomotor restlessness) was reported in 1.5% of bupropion-treated patients. Suicide attempt and completed suicide have occurred in 0.1% to 1% of patients during clinical trial evaluation or postmarketing use of bupropion. Mania can occur in predisposed patients during treatment with an antidepressant. Monitor all antidepressant-treated patients for any indication for worsening of depression or the condition being treated and the emergence of suicidal behaviors or suicidal ideation, especially during the initial few months of drug therapy and after dosage changes. In a pooled analysis of placebo-controlled trials of antidepressants (n = 4,500 pediatrics and 77,000 adults), there was an increased risk for suicidal thoughts and behaviors in patients 24 years of age and younger receiving an antidepressant versus placebo, with considerable variation in the risk of suicidality among drugs. The difference in the absolute risk of suicidal thoughts and behaviors across different indications was highest in those with major depression. No suicides occurred in any of the pediatric trials. These

studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over 24 years of age; there was a reduction in risk with antidepressant use in patients aged 65 and older. A ten-year retrospective postmarketing safety review conducted by the FDA indicated that bupropion smoking cessation products were associated with 46 cases of suicidal ideation and 29 cases of suicidal behavior in patients with a prior psychiatric history (n = 18), without this history (n = 24), or an unknown psychiatric history (n = 33). In the cases of suicidal ideation for which demographics were available, 40% were male, 60% were female, and the median age was 46 years (range 26 to 70 years). In the cases reporting suicidal behavior, 59% were male, 41% were female, and the median age was 35 years (range 15 to 70 years). A significant change in thinking and/or behaviors was reported by 23% of the patients after treatment initiation. Seventy percent of the studied patients also had a diagnosis of depression. Of the cases considered serious (n = 59), outcomes were categorized as follows and were not mutually exclusive: death (17%), hospitalization (36%), life-threatening (27%), disability (8%), intervention required (3%), and other (31%). Caregivers and/or patients should immediately notify the prescriber of changes in behavior or suicidal ideation.

myoclonia, Tourette's syndrome

Frequent neurological adverse events associated with bupropion include myoclonia. During clinical trials, the incidence of myoclonia in bupropion recipients was 1% or more. Individuals with Gilles de la Tourette syndrome or a family history of this syndrome may have motor or phonetic tics unmasked or exacerbated by the use of bupropion for ADHD symptoms. Exacerbation of tics may respond to dosage reduction; in some cases, bupropion may need to be discontinued.

anorexia, appetite stimulation, weight gain, weight loss

Bupropion may cause weight loss. A weight loss of more than 5 pounds (lb.) occurred in 23.2% of patients taking immediate-release bupropion, approximately double that of patients taking tricyclic antidepressants or placebo. Approximately 14% of patients on sustained-release formulations of bupropion lose weight. Roughly 23% of patients receiving bupropion XL enrolled in seasonal affective disorder (SAD) trials had a weight loss of more than 5 lb. vs. 11% with placebo; alternatively, just 11% of bupropion XL patients had a weight gain of more than 5 lb. vs. 21% taking placebo. Weight gain may be associated with untreated depression. In general, weight gain is rare with bupropion treatment; weight gain occurred in 2% to 13.6% of bupropion recipients receiving any formulation/product during clinical trials. The incidence of anorexia reported during trials was similar for patients taking bupropion vs. placebo (roughly 1% to 18%) and may represent a symptom of the depressive illness rather than an adverse event. Although

not as common, appetite stimulation (2% to 3.7%) was also reported with bupropion during clinical trials.

abdominal pain, colitis, constipation, diarrhea, dysgeusia, dyspepsia, dysphagia, elevated hepatic enzymes, esophagitis, flatulence, gastroesophageal reflux, GI bleeding, GI perforation, gingivitis, glossitis, hepatitis, hypersalivation, jaundice, nausea, oral ulceration, pancreatitis, polydipsia, stomatitis, teeth grinding (bruxism), vomiting, xerostomia

During clinical trials of immediate-release or extended-release bupropion formulations, the following gastrointestinal (GI) effects and incidences were reported as greater than placebo and included: dyspepsia (3.1%), nausea (9% to 22.9%), vomiting (2% to 22.9%), diarrhea (4% to 7%), constipation (5% to 26%), xerostomia (10% to 27.6%), hypersalivation (3.4%), dysphagia (0% to 2%), flatulence (6%), abdominal pain (2% to 9%), and dysgeusia (2% to 4%). In a comparative trial of sustained-release bupropion (Zyban) monotherapy for smoking cessation, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, the following GI effects and incidences were reported: nausea (9%, 7%, 11%, 4%), xerostomia (10%, 4%, 9%, 4%), constipation (8%, 4%, 9%, 3%), diarrhea (4%, 4%, 3%, 1%), oral ulceration (2%, 1%, 1%, 1%), abdominal pain (3%, 4%, 1%, 1%), dysgeusia (3%, 1%, 3%, 2%), and thirst (less than 1%, less than 1%, 2%, 0%). During other pre-marketing evaluations, stomatitis was reported in 1% or more of patients. Adverse GI reactions occurring in roughly 0.1% to 1% of patients included teeth grinding (bruxism), elevated hepatic enzymes, jaundice, liver damage, excessive thirst (polydipsia), gastroesophageal reflux, gingivitis, glossitis, and hypersalivation. Rare events in less than 0.1% of patients have included colitis, GI bleeding, GI perforation, and stomach ulcer. GI adverse reactions reported during post-marketing use of bupropion include esophagitis, gum bleeding, hepatitis, and pancreatitis. Due to the voluntary nature of postmarketing reports, neither incidence nor definitive association to bupropion have been established.

AV block, Brugada syndrome, chest pain (unspecified), edema, flushing, hypertension, hypotension, myocardial infarction, orthostatic hypotension, pallor, palpitations, peripheral vasodilation, phlebitis, pulmonary embolism, sinus tachycardia, stroke, syncope

Cardiac toxicity is relatively uncommon for bupropion when compared with tricyclic antidepressants. Hypertension occurred in 1% to 4.3% of patients taking bupropion during clinical trials, compared to 0% to 1.6% taking placebo. New onset or worsening of existing hypertension occurred in a higher percentage of patients (i.e., 6.1%) taking bupropion concurrently with nicotine transdermal systems (NTS) for smoking cessation; in some cases hypertension was severe. Other cardiovascular effects which occurred

more frequently in those receiving bupropion formulations vs. those receiving placebo during clinical trials included: unspecified cardiac arrhythmias (5.3%), dizziness (22.3%), hypotension (2.5%), palpitations (2% to 6%), syncope (1.2%), sinus tachycardia (10.8%), chest pain (unspecified) (less than 1% to 4%) and flushing (1% to 4%). In a comparative trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, respectively, the following cardiac effects and incidences were reported: hypertension (1%, less than 1%, 2%, 0%), palpitations (2%, 0%, 1%, 0%), and chest pain (less than 1%, 1%, 3%, 1%). Edema was reported in 1% or more of patients during pre-marketing evaluation of bupropion and flushing was reported in 1% or less. Cardiac effects reported in 0.1% to 1% of patients included unspecified chest pain, ECG changes or abnormalities (premature beats and nonspecific ST-T changes), dyspnea, orthostatic hypotension, stroke, sinus tachycardia, and peripheral vasodilation. Pallor, phlebitis, syncope, and myocardial infarction rarely occurred (less than 0.1%). Also observed in postmarketing use were complete AV block, extrasystoles, and pulmonary embolism. Drug-induced Brugada syndrome/pattern has also been reported postmarketing with bupropion-containing products.

blurred vision, diplopia, mydriasis, ocular hypertension, xerophthalmia

Blurred vision affected 2% to 14.6% of bupropion-treated patients during clinical trials, compared to 2% to 10.3% taking placebo. Diplopia was reported in 2% to 3% of those receiving active drug versus 2% of those receiving placebo. During other pre-marketing or post-marketing use, blurred vision or diplopia was reported in 1% or more of patients. Other ocular effects that occurred in clinical trials or during post-marketing use included abnormal accommodation (0.1% to 1%), xerophthalmia (0.1% to 1%), ocular hypertension, and mydriasis.

dysmenorrhea, dyspareunia, ejaculation dysfunction, gynecomastia, impotence (erectile dysfunction), libido decrease, libido increase, menstrual irregularity, testicular swelling, vaginal bleeding, vaginal irritation

Twice as many patients taking bupropion reported libido decrease (3.1%) vs. placebo (1.6%). Conversely, libido increase has been reported in 1% or more of patients receiving bupropion. Menstrual irregularity was reported as unspecified menstrual complaints by 4.7% of bupropion-treated patients as dysmenorrhea (2%) and/or as vaginal bleeding (0% to 2%), and at higher incidences vs. placebo. Impotence (erectile dysfunction) occurred in 3.4% and painful erections occurred in 0.1% to 1% of bupropion recipients during clinical trials. Cases of gynecomastia, prostate disorder, and testicular swelling have been reported in 0.1% to 1% of bupropion-treated patients. Other sexual or

reproductive system reactions have also occurred and include ejaculation dysfunction (0.1% to 1%, reported as retarded ejaculation or painful ejaculation), painful erection, dyspareunia (less than 0.1%), salpingitis, and vaginal irritation (0.1% to 1%). Causal effect may be uncertain as trials were not always conducted with adequate controls.

hot flashes

Depending on the dosage form of bupropion used, hot flashes have been reported in 1% to 3% of treated patients; menopause was reported in less than 0.1% of bupropion recipients during clinical trials.

acne vulgaris, acute generalized exanthematous pustulosis (AGEP), alopecia, exfoliative dermatitis, hirsutism, hyperhidrosis, maculopapular rash, photosensitivity, pruritus, rash, urticaria, xerosis

During clinical trials of immediate-release or extended-release bupropion formulations, hyperhidrosis occurred more frequently in the bupropion groups (5% to 22.3%) vs. placebo. Rash (unspecified) (3% to 8%), pruritus (2 to 4%), urticaria (1% to 2%), alopecia (1% or more), and xerosis (2%) were other dermatologic adverse reactions commonly reported by recipients of bupropion. Acne vulgaris (0.1% to 1%), maculopapular rash (less than 0.1%), hirsutism (less than 0.1%), photosensitivity (0.1% to 1%), and exfoliative dermatitis have also occurred infrequently or rarely with bupropion use. Acute generalized exanthematous pustulosis (AGEP) has also been reported with postmarketing use. In a comparative trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, the following dermatologic effects and incidences were reported: rash (4%, 3%, 3%, 2%), pruritus (3%, 1%, 5%, 1%), and urticaria (2%, 0%, 2%, 0%).

glycosuria, hyperglycemia, hypoglycemia, hyponatremia, SIADH

Some endocrine side effects have been reported during postmarketing use of bupropion. These rare endocrine-related side effects have included hyperglycemia, hypoglycemia, glycosuria, hyponatremia, and syndrome of inappropriate antidiuretic hormone (SIADH). Due to the voluntary nature of postmarketing reports, neither causality nor the incidence can be established.

anaphylactic shock, anaphylactoid reactions, angioedema, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), dyspnea, erythema multiforme, serum sickness, Stevens-Johnson syndrome

Rarely, anaphylactoid reactions characterized by symptoms such as rash, pruritus,

urticaria (1% to 2%), angioedema, edema, chest pain, and dyspnea (1%) requiring medical treatment have been reported in clinical trials with bupropion. Most of these events occur in 0.1% to 0.3% or less of patients treated. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome (SJS), and anaphylactic shock associated with bupropion. A case of a serum sickness reaction has also been reported in the literature. Serum-sickness-like reactions consist of delayed hypersensitivity reactions, arthralgia, myalgia, pyrexia, and rash. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported during postmarketing use of bupropion. Bupropion should be promptly discontinued and appropriate medical treatment should be initiated in patients presenting with serious hypersensitivity reactions or symptoms indicative of DRESS in whom an unrelated etiology cannot be identified.

anemia, ecchymosis, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, thrombocytopenia

Hematologic and lymphatic effects reported with bupropion include infrequent cases of ecchymosis (0.1% to 1%). Anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia, pancytopenia, and changes in the INR and/or PT have been noted; the incidence has not been reported. Causality has not been established.

arthralgia, asthenia, back pain, muscle cramps, myalgia, myasthenia, rhabdomyolysis

Musculoskeletal events reported during clinical trials by patients receiving bupropion therapy and at higher incidences than with placebo included arthralgia (1% to 5%), asthenia (2% to 4%), myalgia (2% to 6%), and muscle spasms (1.9%). Other musculoskeletal adverse reactions reported during bupropion use include muscle twitching (1% to 2%), arthritis (0% to 3.1%), neck pain (2%), sciatica (less than 0.1%), pain in extremity (3%), and pain (unspecified) at 2% to 3%). In a comparative trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, the following musculoskeletal effects and incidences were reported: myalgia (4%, 3%, 5%, 3), arthralgia (5%, 3%, 3%, 2%), and neck pain (2%, 1%, less than 1%, 0%). Musculoskeletal effects reported in 0.1% to 1% of patients receiving bupropion during premarketing or postmarketing use included leg muscle cramps, back pain, inguinal hernia, and muscle twitching. Musculoskeletal chest pain was reported in 1% or less of patients and sciatica rarely occurred (less than 0.1%). Arthralgia, myalgia, muscle weakness (myasthenia), and muscle rigidity with increased temperature and rhabdomyolysis have been reported during postmarketing use.

bronchospasm, chills, cough, epistaxis, fever, infection, influenza, malaise, nasal congestion, pharyngitis, rhinitis, sinusitis

Infections (overall incidence 8% to 9% vs. 6% for placebo) have been reported by bupropion recipients during clinical trials. The types of infection in treated patients included upper respiratory tract infections (5% to 9%) [e.g., sinusitis (1% to 5%), pharyngitis (3% to 13%), bronchitis (2%), pneumonia (less than 0.1%)], urinary tract infections (1%), pelvic infections (less than 0.1%), and influenza (2% or more). Symptoms reported during use of bupropion that may be associated with these infections included rhinitis (12%), epistaxis (2%), increased cough (1% to 4%), nasal congestion (2% or more), sinus congestion (2% or more), pharyngolaryngeal pain (2% or more), malaise (less than 0.1%), fever (1% to 2%), fever/chills (1.2%), and bronchospasm (less than 0.1%). In a comparative trial of sustained-release bupropion (Zyban) monotherapy, nicotine transdermal system (NTS) monotherapy, Zyban/NTS combination, or placebo, the following effects and incidences were reported: rhinitis (12%, 11%, 9%, 8%), increased cough (3%, 5%, less than 1%, 1%), pharyngitis (3%, 2%, 3%, 0%), sinusitis (2%, 2%, 2%, 1%), dyspnea (1%, 0%, 2%, 1%), and epistaxis (2%, 1%, 1%, 0%).

dental pain, drug-induced body odor, fatigue, hair discoloration, peripheral edema

Adverse reactions reported by recipients of bupropion during premarketing or postmarketing use, and not discussed elsewhere in the monograph, include peripheral edema (0.1% to 1%), fatigue (5%), dental pain (0.1% to 1%), drug-induced body odor (less than 0.1%), facial edema (0.1% to 1%), and hair discoloration (less than 0.1%). Facial edema was also reported in a comparative trial of sustained-release bupropion (Zyban) monotherapy (less than 1%), nicotine transdermal system (NTS) monotherapy (0%), Zyban/NTS combination (1%), or placebo (0%).

cystitis, dysuria, increased urinary frequency, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency

Urinary tract reactions reported more frequently with immediate-release or extended-release bupropion formulations than placebo during clinical trials included: increased urinary frequency (2% to 5%), urinary urgency (less than 0.5% to 2%), urinary retention (1.9%), and urinary tract infection (0% to 1%). Nocturia and urinary frequency occurred in 1% or more of bupropion-treated patients during premarketing evaluation. Polyuria, urinary urgency, and prostate disorder were reported in 0.1% to 1%. Cystitis and dysuria rarely occurred (less than 0.1%). Also observed postmarketing: cystitis, dysuria, urinary incontinence, and urinary retention; however, the frequencies have not been reported.

akinesia, dyskinesia, dystonic reaction, hyperkinesis, hypertonia, pseudoparkinsonism, tardive dyskinesia

During clinical trials of immediate-release or extended-release bupropion formulations, the following extrapyramidal symptoms occurred in the bupropion groups at similar incidences to placebo: bradykinesia (8%), and pseudoparkinsonism (1.5%). Extrapyramidal syndrome (unspecified) has been reported during use of bupropion. Extrapyramidal symptoms that have occurred in 1% or more of patients during pre-marketing evaluation include dystonic reaction and dyskinesia. Hyperkinesis and hypertonia have been reported in 0.1% to 1% of patients. Akinesia, hypokinesia, dystonia, dyskinesia, pseudoparkinsonism, and unmasking of tardive dyskinesia have also occurred during postmarketing use; however, the incidences are unknown.

hearing loss, tinnitus

During clinical trials of immediate-release or extended-release bupropion formulation, tinnitus was reported more frequently in patients receiving bupropion than placebo (3% to 6%). Unspecified sensory disturbance (4%), auditory or hearing disturbance (5.3%), and gustatory disturbance (3.1%) were also reported more frequently in bupropion active treatment groups than placebo groups. Tinnitus occurred during a comparative trial of sustained-release bupropion (Zyban) monotherapy (1%), nicotine transdermal system (NTS) monotherapy (0%), Zyban/NTS combination (less than 1%), and placebo (0%). During pre-marketing or post-marketing use of bupropion, deafness (hearing loss) has been reported.

neonatal abstinence syndrome

While not reported for bupropion, a neonatal abstinence syndrome has been reported in infants exposed to certain antidepressants in utero. After birth, symptoms consistent with withdrawal (i.e., poor feeding, hypoglycemia, hypothermia, lethargy or irritability, vomiting, etc.) were noted. Such complications can arise immediately upon delivery. In some reports, serum concentrations of the agent were measurable in the infants affected, so the symptoms may have been due to a direct adverse effect of the antidepressant. The physician should carefully consider the potential risks and benefits of treatment. If clinically feasible, and taking the drug half-life into consideration, appropriate tapering of the agent prior to delivery may be considered as an alternative.

euphoria

Euphoria was reported more frequently with immediate-release or extended-release bupropion formulations than placebo during clinical trial evaluation (1.2% vs. 0.5%). During controlled trials in patients with a history of multiple substance abuse, normal volunteers, and depressed patients, there was an increase in motor activity and

agitation/excitement. In a single dose study of bupropion 400 mg in a population of individuals experienced with drugs of abuse, a mild amphetamine-like activity was produced 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. Although use of recommended daily dosages of bupropion when administered in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers, higher doses (that could not be tested because of seizure risk) could theoretically be modestly attractive to those who abuse CNS stimulant drugs. In addition, the inhalation of crushed tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported when bupropion has been administered intranasally or by parenteral injection.

serotonin syndrome

In an ISMP safety report, bupropion was noted as 1 of the 19 overall drugs and one of the 9 antidepressants having the strongest signals for serotonin syndrome with 18 cases reported over 1 year to the FDA Adverse Event Reporting System (FAERS). Serotonin syndrome rarely happens with single drug therapy, and more commonly is reported with interactions between multiple serotonergic drugs or accidental or intentional drug overdoses. How bupropion might promote serotonergic excess is unclear, as bupropion is a relatively weak inhibitor of the neuronal reuptake of norepinephrine and dopamine, and does not inhibit the reuptake of serotonin. Bupropion does not inhibit monoamine oxidase. The manufacturers have not reported serotonin syndrome as a postmarketing event.

laboratory test interference

Laboratory test interference has been reported with bupropion use. False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. The false-positive result 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.

Description

Bupropion is an oral aminoketone antidepressant medication that is unrelated to other known antidepressants. Bupropion was initially approved for treatment of depression in 1985 but was removed from market for several years due to concerns for drug-induced seizures. Bupropion was reintroduced as a treatment for major depressive disorder in

an immediate-release form (Wellbutrin) and was later approved in a twice-daily sustained-release formulation (Wellbutrin SR) and a once-daily formulation (Wellbutrin XL) for treatment of depression in adults and for treatment of depressive episodes in adults with a history of seasonal affective disorder (SAD). A once-daily formulation of bupropion hydrobromide (Aplenzin) is also approved for the treatment of major depression and depressive episodes in patients with SAD. A sustained-release formulation is approved for use as an aid in smoking cessation (Zyban) and may be used as monotherapy or in combination with nicotine transdermal systems (NTS). Guidelines support burropion use for smoking cessation in adults, including use beyond 12 weeks to maintain abstinence if needed. Bupropion has limited data for the treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients. Bupropion has been used off-label for other conditions, including neuropathic pain and ADHD in adults. Bupropion carries a dose-related risk for seizures. Given the multiple products available with different indications, it is important to use care in product selection and to not duplicate bupropion prescriptions, which could lead to overdosage. Additionally, all product labels for antidepressants contain a boxed warning related to an increased risk of suicidality in children, adolescents, and young adults during the initial stages of therapy when treating depression or other conditions (e.g., smoking cessation); therefore, the necessity of pharmacologic therapy versus the potential risks should be carefully considered in these populations.

Mechanism Of Action

The action of bupropion in the treatment of major depressive disorder and seasonal affective disorder is not fully understood, but is likely related to dual-reuptake inhibition of dopamine and norepinephrine. This reuptake inhibition is associated with increased synaptic levels of dopamine and norepinephrine in the brain, particularly within the nucleus accumbens and the prefrontal cortex. In contrast to most antidepressants, bupropion does not inhibit monoamine oxidase or the reuptake of serotonin and does not have appreciable activity at histamine, acetylcholine, or alpha- or beta-adrenergic receptors. The unique activity of bupropion allows for use as monotherapy for depression as well as an add-on treatment option for partial responders. Antidepressant activity is usually noted within 1 to 3 weeks of initiation of bupropion treatment; full effects may not be seen until 4 weeks of therapy.

The specific mechanism by which bupropion enhances the ability to abstain from tobacco smoking is likely also related to the inhibition of noradrenergic and dopaminergic neuronal reuptake. The resultant increase in norepinephrine may attenuate nicotine withdrawal symptoms, while increased dopamine at neuronal sites may reduce nicotine cravings and the urge to smoke. Because the attainment of steady-state blood levels requires approximately 1 week of treatment, patients should start

bupropion 1 to 2 weeks prior to their "target quit date". In smoking cessation, the ability to abstain from smoking continuously through the seventh week of bupropion therapy is associated with maintenance of long-term abstinence. Patients who have not stopped smoking after 7 to 12 weeks of treatment are generally considered non-responsive to bupropion treatment.

Pharmacokinetics

Bupropion is administered orally as the hydrochloride salt (Wellbutrin, Wellbutrin SR, Wellbutrin XL, Zyban, Forfivo XL) or hydrobromide salt (Aplenzin). Bupropion is a racemic mixture; however, the pharmacologic actions and pharmacokinetics of the individual enantiomers have not been evaluated. The drug readily crosses the blood-brain barrier. Plasma protein binding is about 84%. Metabolism takes place in the liver, producing several metabolites; the 3 major active metabolites are hydroxybupropion, threohydrobupropion, and erythrohydrobupropion. CYP2B6 is involved in forming hydroxybupropion, the major metabolite. All active metabolites are present in higher concentrations in the plasma than the parent compound. In mice, hydroxybupropion appears to have one-half the potency of bupropion; the other metabolites are one-tenth to one-half as potent. Bupropion appears to induce its own metabolism, but this does not appear to be clinically significant. The terminal elimination half-life of immediate-release bupropion is approximately 14 hours with a range of 8 to 24 hours. The terminal elimination half-life of the sustained-release hydrochloride product and the extended-release hydrobromide product is roughly 21 hours. Half-lives for hydroxybupropion, erythrohydroxybupropion, and threohydroxybupropion are 20 hours, 33 hours, and 37 hours, respectively. Less than 1% is excreted unchanged in the urine. Over 60% is excreted as metabolites in the urine within 24 hours; over 80% is eliminated in 96 hours. Less than 10% of metabolites are excreted in the feces. Steady-state concentrations of bupropion and its metabolites are achieved in 5 to 8 days; however, antidepressant effects have an onset of roughly 1 to 3 weeks.

Affected cytochrome P450 (CYP450) isoenzymes and drug transporters: CYP2D6, CYP2B6, OCT2
Because of the extensive metabolism of bupropion by CYP2B6, clinically significant drug interactions are possible with drugs that are metabolized by or are inhibitors or inducers of this isoenzyme. In vitro data indicate that bupropion and hydroxybupropion are inhibitors of CYP2D6. In vitro, bupropion and its 3 metabolites are inhibitors of the renal organic transporter OCT2 to a clinically significant extent; however, in vivo drug interaction studies have not found clinically significant drug-drug interactions with OCT-2 substrates.

Route-Specific Pharmacokinetics

- **Oral Route**

Based on animal data, the oral bioavailability is roughly 5% to 20%; oral bioavailability in humans has not been determined.

Wellbutrin, Wellbutrin SR, and Wellbutrin XL (bupropion hydrochloride): Bupropion XL has been found to be bioequivalent to the immediate-release tablet, sustained-release tablet, and extended-release hydrobromide tablet. In studies of healthy volunteers, administration with food increased Cmax and AUC by 11% to 35% and 16% to 19%, respectively. These changes are not considered clinically significant; therefore, bupropion can be taken with or without food. Peak plasma concentrations are achieved within 1.5 hours after administration of immediate-release bupropion, and within 3 hours after administration of sustained-release hydrochloride formulations. Peak plasma concentrations of the active metabolite hydroxybupropion occur about 3 hours after administration of immediate-release bupropion. Peak plasma concentrations of hydroxybupropion are about 10 times those of bupropion at steady state. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg; however, it is not known if the proportionality between dose and plasma levels are maintained in chronic use.

Aplenzin (bupropion hydrobromide): Peak plasma concentrations are achieved within approximately 5 hours after administration of the hydrobromide tablet. Peak plasma concentrations of the active metabolite hydroxybupropion occur about 6 hours after administration. Peak plasma concentrations of hydroxybupropion are about 10 times those of bupropion at steady state. The molecular weight of the hydrobromide salt of bupropion is higher than the hydrochloride (HCl) salt; therefore, a larger total mg dose is needed to provide the same amount of active drug as HCl dosage forms.

Forfivo XL (bupropion hydrochloride): Following a single dose of Forfivo XL, a 450 mg extended-release bupropion tablet formulation, the median time to peak plasma concentrations is about 5 hours under fasting conditions and 12 hours under fed conditions. The mean systemic exposure to bupropion is increased by 25% when taken with food. Peak plasma concentrations of hydroxybupropion occur about 10 hours after a dose of Forfivo XL under fasting conditions and 16 hours under fed conditions. The food effect is not considered clinically significant; therefore, Forfivo XL may be taken without regard to meals. In a single dose study under fasting conditions, one 450 mg dose of Forfivo XL was equivalent to a dose consisting of three 150 mg tablets of Wellbutrin XL.

- **Hepatic Impairment**

Half-lives of bupropion and/or its major metabolites are prolonged in patients with alcoholic liver disease, cirrhosis, or left-ventricular dysfunction. In patients with hepatic disease, the mean AUC increased by roughly 1.5-fold for hydroxybupropion and roughly 2.5-fold for threo/erythrohydrobupropion. The median Tmax 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. Dosage adjustment is required in patients with hepatic dysfunction. Use of Forfivo XL, a 450 mg extended-release tablet formulation, is not recommended in patients with hepatic impairment, as the dose is fixed and no lower strength is available.

- **Renal Impairment**

An inter-study comparison of healthy subjects and those with end-stage renal failure showed that although the elimination of the parent compound was similar between groups, the Cmax and AUC of bupropion's active metabolites were increased in the renal failure group. In a separate study of patients with moderate to severe renal impairment, bupropion exposure after administration of the sustained-release product was about 2-fold higher in the renally impaired group than in normal subjects, while concentrations of the active metabolites of bupropion and placebo were similar. The clinical impact of these findings, if any, have not been described. Use of Forfivo XL, a 450 mg extended-release tablet formulation, is not recommended in patients with renal impairment as the dose is fixed and lower dosage strengths are not available.

- **Pediatrics**

Adolescents have been shown to metabolize bupropion SR to its active metabolites more rapidly than adults. Areas under the concentration curves for the hydroxybupropion, threohydrobupropion, and erythrohydrobupropion were 20, 12, and 2.7 times higher, respectively, than for bupropion. Relative to adults, the mean half-lives of bupropion (12.1 h) and threohydrobupropion (26.3 h) were significantly shorter, and AUC ratios of metabolites to bupropion were 19 to 80% higher. Until the clinical importance of bupropion's metabolites is clarified, bupropion SR should be given in divided doses to adolescents.

Administration

For storage information, see the specific product information within the How Supplied section.

Oral Administration

NOTE: Given that there are multiple dosing regimens and 2 salt forms of bupropion available, ensure the selection of the correct product for administration. Patients should not be prescribed more than 1 bupropion product to avoid duplication of treatment and overdosage, which may result in seizures and other serious adverse effects.
May administer with or without food.

Oral Solid Formulations

Immediate-release bupropion hydrochloride tablets (e.g., Wellbutrin):
It is advisable to separate doses by at least 6 hours. The total daily dose is usually administered in 3 divided doses.

Sustained-release bupropion hydrochloride tablets (e.g., Wellbutrin SR):
It has been suggested that the tablets may be cut in half once, if needed, just prior to administration ; however, the manufacturer states that the tablets should be swallowed whole and should not be cut, chewed, or crushed since this may lead to an increased risk of adverse effects including seizures.
If multiple doses are administered daily, each dose should be given at least 8 hours apart.

Extended-release bupropion hydrochloride tablets (e.g., Wellbutrin XL, Forfivo XL):
Swallow tablets whole. Do not chew, cut, or crush tablets since this may lead to an increased risk of adverse effects including seizures.
Administer once daily, preferably in the morning.

Sustained-release bupropion hydrochloride tablets (Smoking cessation) (e.g., Zyban):
Do not crush, divide, or chew tablets; swallow whole.
The total daily dose is usually administered in two divided doses. Each dose should be given at least 8 hours apart.

Bupropion hydrobromide extended-release tablets (i.e., Aplenzin):
Swallow tablets whole. Do not chew, cut, or crush tablets.
Administer once daily in the morning.

Maximum Dosage Limits

- **Adults**
  Immediate-release tablets: 450 mg/day PO, no single dose should exceed 150 mg.
  Wellbutrin SR: 400 mg/day PO; no single dose should exceed 200 mg.
  Zyban: 300 mg/day PO for smoking cessation; no single dose should exceed 150 mg.
  Wellbutrin XL: 450 mg/day PO.
  Aplenzin: 522 mg/day PO; no single dose should exceed 522 mg.
  Forfivo XL: 450 mg/day PO.
- **Geriatric**
  Immediate-release tablets: 450 mg/day PO, no single dose should exceed 150 mg.
  Wellbutrin SR: 400 mg/day PO; no single dose should exceed 200 mg.

Zyban: 300 mg/day PO for smoking cessation; no single dose should exceed 150 mg.
Wellbutrin XL: 450 mg/day PO.
Aplenzin: 522 mg/day PO; no single dose should exceed 522 mg.
Forfivo XL: 450 mg/day PO.

- **Adolescents**
  Safety and efficacy have not been established; however, a total daily dosage up to 300 mg/day PO for immediate-release tablets has been suggested for the treatment of attention-deficit hyperactivity disorder (ADHD); doses up to 6 mg/kg/day (not to exceed 300 or 400 mg/day) PO of the bupropion SR products have been used in studies for treatment of depression.
- **Children**
  6 to 12 years: Safety and efficacy have not been established; however, a total daily dosage up to 300 mg/day PO for immediate-release tablets has been suggested for the treatment of attention-deficit hyperactivity disorder (ADHD).
  5 years and younger: Safety and efficacy have not been established.
- **Infants**
  Safety and efficacy have not been established.
- **Neonates**
  Safety and efficacy have not been established.

Dosage Forms

- Aplenzin 174mg Extended-Release Tablet (Once Daily)
- Aplenzin 348mg Extended-Release Tablet (Once Daily)
- Aplenzin 522mg Extended-Release Tablet (Once Daily)
- Bupropion Hydrochloride 100mg Oral tablet [Depression/Mood Disorders]
- Bupropion Hydrochloride 100mg Oral tablet, extended release 12 hour [Depression/Mood Disorders]
- Bupropion Hydrochloride 150mg Oral tablet, extended release 12 hour [Depression/Mood Disorders]
- Bupropion Hydrochloride 150mg Oral tablet, extended release 12 hour [Smoking Cessation]
- Bupropion Hydrochloride 150mg Oral tablet, extended release 24 hour [Depression/Mood Disorders]
- Bupropion Hydrochloride 200mg Oral tablet, extended release 12 hour [Depression/Mood Disorders]
- Bupropion Hydrochloride 300mg Oral tablet, extended release 24 hour [Depression/Mood Disorders]

- Bupropion Hydrochloride 450mg Oral tablet, extended release 24 hour [Depression/Mood Disorders]
- Bupropion Hydrochloride 75mg Oral tablet [Depression/Mood Disorders]
- Bupropion Hydrochloride Bulk powder
- Wellbutrin SR 100mg Extended-Release Tablet
- Wellbutrin SR 150mg Extended-Release Tablet
- Wellbutrin SR 200mg Extended-Release Tablet
- Wellbutrin XL 150mg Extended-Release Tablet
- Wellbutrin XL 150mg Extended-Release Tablet
- Wellbutrin XL 300mg Extended-Release Tablet
- Wellbutrin XL 300mg Extended-Release Tablet

Dosage Adjustment Guidelines

Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh Score 7 to 15), initiate therapy at a lower dosage and do not exceed 75 mg/day PO of immediate-release Wellbutrin, 100 mg/day or 150 mg every other day of Wellbutrin SR, 150 mg every other day of Zyban or Wellbutrin XL, or 174 mg every other day of Aplenzin. Consider reduced dosage or dosage frequency in patients with mild hepatic impairment (Child-Pugh Score 5 to 6); however, no guidelines are available. Use of Forfivo XL, a 450 mg extended-release tablet formulation, is not recommended in patients with hepatic impairment since there is no lower dose strength.

Renal Impairment

CrCl less than 90 mL/minute: Consider reduced dosage and/or dosage frequency but specific recommendations are not available. Bupropion and its metabolites are renally eliminated and may accumulate in patients with renal impairment. Use of Forfivo XL, a 450 mg extended-release tablet formulation, is not recommended because there is no lower dose strength.