HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FORFIVO XL (bupropion hydrochloride extended-release tablets), for oral use

Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

See full prescribing information for complete boxed warning

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **Serious neuropsychiatric events have been reported in patients taking bupropion for smoking cessation (5.2).**

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

Dosage and Administration, Discontinuation (2.4)	08/2016
Dosage and Administration, Switching To/From MAOIs (2.7)	08/2016
Dosage and Administration, Use with Reversible MAOIs (2.8)	08/2016
Contraindications, MAOIs (4)	08/2016
Warnings and Precautions, Neuropsychiatric Symptoms (5.2)	08/2016
Warnings and Precautions, Seizure (5.3)	08/2016
Warnings and Precautions, Hypertension (5.4)	08/2016

----------INDICATIONS AND USAGE----------

FORFIVO XL is an aminoketone antidepressant indicated for the treatment of major depressive disorder (MDD) (1). The efficacy was established in two 4-week trials, one 6-week trial with bupropion immediate-release formulation, and one maintenance trial with bupropion sustained-release formulation, all in adults (14). Periodically re-evaluate long-term usefulness for the individual patient (1).

----------DOSAGE AND ADMINISTRATION----------

- Use one tablet (450 mg) once daily without regard to food (2.1).
- Swallow the tablet whole. Do not chew, divide, or crush (2.1).
- Do not initiate treatment with FORFIVO XL. Use another bupropion formulation for initial dose titration (2.2).
- Can be used in patients who are receiving 300 mg/day of another bupropion formulation for at least 2 weeks, and require a dosage of 450 mg/day (2.2).
- Patients who are currently being treated with other bupropion products at 450 mg/day can be switched to equivalent dose of FORFIVO XL once daily (2.2).

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

- Extended-release tablets: 450 mg (3)

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

- Seizure disorder (4, 5.3)
- Current use of other bupropion products (4, 5.3)
- Current or prior diagnosis of bulimia or anorexia nervosa (4, 5.3)
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs (4, 5.3)
- *Monoamine Oxidase Inhibitors (MAOIs):* Do not use MAOIs intended to treat psychiatric disorders with FORFIVO XL or within 14 days of stopping treatment with FORFIVO XL. Do not use FORFIVO XL within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start FORFIVO XL in a patient who is being treated with linezolid or intravenous methylene blue (4, 7.6).
- Known hypersensitivity to bupropion or other ingredients of FORFIVO XL (4, 5.8)

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

- *Seizure Risk:* The risk is dose dependent. Discontinue if seizure occurs (4, 5.3, 7.3).
- *Hypertension:* FORFIVO XL can increase blood pressure. Monitor blood pressure before initiating treatment and periodically during treatment (5.4).
- *Activation of Mania/Hypomania:* Screen patients for bipolar disorder and monitor for these symptoms (5.5).
- *Psychosis and Other Neuropsychiatric Reactions:* Discontinue if such reactions occur (5.6).
- *Angle-closure Glaucoma:* Angle-closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants (5.7).

----------ADVERSE REACTIONS----------

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

To report SUSPECTED ADVERSE REACTIONS, contact Edgemont Pharmaceuticals, LLC at 1-888- 594-4332 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- *CYP2B6 Inhibitors:* Ticlopidine or clopidogrel may increase bupropion exposure. Coadministration of FORFIVO XL with ticlopidine or clopidogrel is not recommended (7.1).
- *CYP2B6 Inducers:* Dose increase may be necessary if coadministered with CYP2B6 inducers (eg, ritonavir, lopinavir, efavirenz, carbamazepine, phenobarbital, and phenytoin) based on clinical exposure, but should not exceed the maximum recommended dose (7.1).
- *Drugs Metabolized by CYP2D6:* Bupropion inhibits CYP2D6 and can increase concentrations of: antidepressants (eg, venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (eg, haloperidol, risperidone, thioridazine), beta-blockers (eg, metoprolol), and Type 1C antiarrhythmics (eg, propafenone, flecainide). Consider dose reduction when using with bupropion (7.2).
- *Drugs That Lower Seizure Threshold:* Dose FORFIVO XL with extreme caution (5.3, 7.3).
- *Dopaminergic Drugs (levodopa and amantadine):* CNS toxicity can occur when used concomitantly with FORFIVO XL (7.4).
- *MAOIs:* Increased risk of hypertensive reactions can occur when used concomitantly with FORFIVO XL (7.6).
- *Drug-Laboratory Test Interactions:* FORFIVO XL can cause false-positive urine test results for amphetamines (7.7).

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

- *Pregnancy:* Use only if benefit outweighs potential risk to the fetus (8.1).
- *Renal Impairment:* Because there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with renal impairment (8.6).
- *Hepatic Impairment:* Because there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with hepatic impairment (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS; AND NEUROPSYCHIATRIC REACTIONS

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects aged 65 and older [see *Warnings and Precautions (5.1)*].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. FORFIVO XL is not approved for use in pediatric patients [see *Warnings and Precautions (5.1)*].

NEUROPSYCHIATRIC REACTIONS IN PATIENTS TAKING BUPROPION FOR SMOKING CESSATION

Serious neuropsychiatric reactions have occurred in patients taking bupropion for smoking cessation [see *Warnings and Precautions (5.2)*]. The majority of these reactions occurred during bupropion treatment, but some occurred in the context of discontinuing treatment. In many cases, a causal relationship to bupropion treatment is not certain, because depressed mood may be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking bupropion who continued to smoke. Although FORFIVO XL is not approved for smoking cessation, observe all patients for neuropsychiatric reactions. Instruct the patient to contact a healthcare provider if such reactions occur [see *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

FORFIVO XL (bupropion hydrochloride extended-release tablets) is indicated for the treatment of major depressive disorder (MDD), as defined by the Diagnostic and Statistical Manual (DSM).

The efficacy of the immediate-release formulation of bupropion was established in two 4-week controlled inpatient trials and one 6-week controlled outpatient trial of adult patients with MDD. The efficacy of the sustained-release formulation of bupropion in the maintenance treatment of MDD was established in a long-term (up to 44 weeks), placebo-controlled trial in patients who had responded to bupropion in an 8-week study of acute treatment [see *Clinical Studies (14)*].

The physician who elects to use FORFIVO XL for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions for Use

One tablet (450 mg) of FORFIVO XL should be taken once daily without regard to meals. FORFIVO XL should be swallowed whole and not crushed, divided, or chewed.

2.2 Initial Treatment with FORFIVO XL

Do not initiate treatment with FORFIVO XL because the 450-mg tablet is the only available dose formulation. Use another bupropion formulation for initial dose titration (referring to prescribing information of other bupropion products).

FORFIVO XL can be used in patients who are receiving 300 mg/day of another bupropion formulation for at least 2 weeks, and require a dosage of 450 mg/day.

Patients who are currently being treated with other bupropion products at 450 mg/day can be switched to an equivalent dose of FORFIVO XL once daily.

2.3 Maintenance Treatment with FORFIVO XL

It is generally agreed that acute episodes of depression require several months or longer of sustained antidepressant treatment beyond the response in the acute episode. It is unknown whether the 450-mg dose needed for maintenance treatment is identical to the dose that provided an initial response. Periodically reassess the need for maintenance treatment and the appropriate dose for such treatment.

2.4 To Discontinue FORFIVO XL, Taper the Dose

Because the 450-mg tablet is the only available dose formulation, use another bupropion formulation for tapering the dose prior to discontinuation (referring to prescribing information of other bupropion products).

2.5 Patients with Impaired Hepatic Function

Because there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with hepatic impairment [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

2.6 Patients with Impaired Renal Function

Because there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with renal impairment [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.7 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Antidepressant

At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with FORFIVO XL. Conversely, at least 14 days should be allowed after stopping FORFIVO XL before starting an MAOI antidepressant [see *Contraindications (4)* and *Drug Interactions (7.6)*].

2.8 Use of FORFIVO XL with Reversible MAOIs Such as Linezolid or Methylene Blue

Do not start FORFIVO XL in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue. Drug interactions can increase the risk of hypertensive reactions. In a patient who requires more urgent treatment of a psychiatric condition, nonpharmacological interventions, including hospitalization, should be considered [see *Contraindications (4)*].

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

The risk of administering methylene blue by nonintravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with FORFIVO XL is unclear. The clinician should, nevertheless, be aware of the possibility of a drug interaction with such use [see *Contraindications (4)* and *Drug Interactions (7.6)*].

3 DOSAGE FORMS AND STRENGTHS

FORFIVO XL Extended-Release Tablets, 450 mg of bupropion hydrochloride, are white to off-white, oval tablets with the logo “Forfivo” printed on one side.

4 CONTRAINDICATIONS

- FORFIVO XL is contraindicated in patients with a seizure disorder [see *Warnings and Precautions (5.3)*].
- FORFIVO XL is contraindicated in patients treated currently with other bupropion products because the incidence of seizure is dose dependent [see *Warnings and Precautions (5.3)*].
- FORFIVO XL is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because a higher incidence of seizures was observed in such patients treated with bupropion [see *Warnings and Precautions (5.3)*].

- FORFIVO XL is contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs [see *Warnings and Precautions (5.3)* and *Drug Interactions (7.3)*].
- The use of MAOIs (intended to treat psychiatric disorders) concomitantly with FORFIVO XL or within 14 days of discontinuing treatment with FORFIVO XL is contraindicated. There is an increased risk of hypertensive reactions when FORFIVO XL is used concomitantly with MAOIs. The use of FORFIVO XL within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting FORFIVO XL in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated [see *Dosage and Administration (2.8)*, *Warnings and Precautions (5.4)*, and *Drug Interactions (7.6)*].
- FORFIVO XL is contraindicated in patients with known hypersensitivity to bupropion or the other ingredients of FORFIVO XL tablets. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported [see *Warnings and Precautions (5.8)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1.	**Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-controlled Trials of Antidepressants in Pediatric and Adult Patients**
Age Range (Years)	**Drug–Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
Increases Compared to Placebo	
< 18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥ 65	6 fewer cases

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

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

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

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

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

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers [see ***Patient Counseling***

***Information (17)*]. Prescriptions for FORFIVO XL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.**

5.2 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

FORFIVO XL is not approved for smoking cessation treatment, but bupropion hydrochloride sustained-release is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation**.** These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide [see *Boxed Warning* and *Adverse Reactions (6.2)*]. Observe patients for the occurrence of neuropsychiatric reactions. Instruct patients to contact a healthcare professional if such reactions occur.

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

5.3 Seizure

Bupropion can cause seizure. The risk of seizure is dose related. FORFIVO XL should be discontinued and not restarted in patients who experience a seizure while on treatment.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. Consider these risks before initiating treatment with FORFIVO XL. FORFIVO XL is contraindicated in patients with a seizure disorder or conditions that increase the risk of seizure (eg, severe head injury, arteriovenous malformation, central nervous system [CNS] tumor or CNS infection, severe stroke, anorexia nervosa or bulimia, or abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs) [see *Contraindications (4)*]. The following conditions can also increase the risk of seizure: concomitant use of other medications that lower the seizure threshold (eg, other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic disorders (eg, hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), or use of illicit drugs (eg, cocaine) or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin, use of anorectic drugs, excessive use of alcohol, use of benzodiazepines, sedatives/hypnotics, or opiates.

Incidence of Seizure with Bupropion Use

The incidence of seizure with bupropion extended-release has not been formally evaluated in clinical trials. In studies using bupropion hydrochloride sustained-release up to 300 mg/day, the incidence of seizure was approximately 0.1% (1/1000 patients). In a large prospective, follow-up study, the seizure incidence was approximately 0.4% (13/3200 patients) with bupropion hydrochloride immediate-release in the range of 300 to 450 mg/day.

Additional data accumulated for bupropion immediate-release suggests that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600-mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of FORFIVO XL. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing.

5.4 Hypertension

Treatment with FORFIVO XL can result in elevated blood pressure and hypertension. Assess blood pressure before initiating treatment with FORFIVO XL, and monitor periodically during treatment. The risk of hypertension is increased if FORFIVO XL is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity [see *Contraindications (4)*].

Data from a comparative trial of the sustained-release formulation of bupropion hydrochloride, nicotine transdermal system (NTS), the combination of sustained-release bupropion hydrochloride plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion hydrochloride and NTS. In this trial, 6.1% of subjects treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of sustained-release bupropion and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with sustained-release bupropion or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

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

5.5 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic manic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. Prior to initiating FORFIVO XL, screen patients for a history of bipolar disorder and the presence of risk factors for bipolar disorder (eg, family history of bipolar disorder, suicide, or depression). FORFIVO XL is not approved for the treatment of bipolar depression.

5.6 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with bupropion have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these

symptoms abated upon dose reduction and/or withdrawal of treatment. Discontinue FORFIVO XL if these reactions occur.

5.7 Angle-closure Glaucoma

Angle-closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs including FORFIVO XL may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.8 Hypersensitivity Reactions

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

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

6 ADVERSE REACTIONS

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

- Suicidal thoughts and behaviors in children, adolescents, and young adults [see *Warnings and Precautions (5.1)*]
- Neuropsychiatric symptoms and suicide risk in smoking cessation treatment [see *Warnings and Precautions (5.2)*]
- Seizure [see *Warnings and Precautions (5.3)*]
- Hypertension [see *Warnings and Precautions (5.4)*]
- Activation of mania or hypomania [see *Warnings and Precautions (5.5)*]
- Psychosis and other neuropsychiatric events [see *Warnings and Precautions (5.6)*]
- Angle-closure Glaucoma [see *Warnings and Precautions (5.7)*]
- Hypersensitivity reactions [see *Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly Observed Adverse Reactions in Controlled Clinical Trials of Sustained-release Bupropion Hydrochloride

Adverse reactions that occurred in at least 5% of patients treated with bupropion hydrochloride sustained-release (300 and 400 mg/day) and at a rate at least twice the placebo rate are listed below.

300 mg/day of bupropion hydrochloride sustained-release: anorexia, dry mouth, rash, sweating, tinnitus, and tremor.

400 mg/day of bupropion hydrochloride sustained-release: abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency.

FORFIVO XL is bioequivalent to three 150-mg tablets of WELLBUTRIN XL®, which has been demonstrated to have similar bioavailability both to the immediate-release and the sustained-release formulations of bupropion. The information included under this subsection and under subsection 6.2 is based primarily on data from controlled clinical trials with the sustained-release and extended-release formulations of bupropion hydrochloride.

Major Depressive Disorder

Adverse Reactions Leading to Discontinuation of Treatment with Bupropion Hydrochloride Immediate-release, Bupropion Hydrochloride Sustained-release, and Bupropion Hydrochloride Extended-release Formulations in Major Depressive Disorder Trials

In placebo-controlled clinical trials with bupropion hydrochloride sustained-release, 4%, 9%, and 11% of the placebo, 300 mg/day, and 400 mg/day groups, respectively, discontinued treatment because of adverse reactions. The specific adverse reactions leading to discontinuation in at least 1% of the 300-mg/day or 400-mg/day groups and at a rate at least twice the placebo rate are listed in *Table 2*.

Table 2.	**Treatment Discontinuation Due to Adverse Reactions in Placebo-controlled Trials in Major Depressive Disorder**		
Adverse Reaction Term	**Placebo (N = 385)**	**Bupropion Hydrochloride Sustained-release 300 mg/day (N = 376)**	**Bupropion Hydrochloride Sustained-release 400 mg/day (N = 114)**
Rash	0.0%	2.4%	0.9%
Nausea	0.3%	0.8%	1.8%
Agitation	0.3%	0.3%	1.8%
Migraine	0.3%	0.0%	1.8%

In clinical trials with bupropion hydrochloride immediate-release, 10% of patients and volunteers discontinued due to an adverse reaction. Reactions resulting in discontinuation (in addition to

those listed above for the sustained-release formulation) included vomiting, seizures, and sleep disturbances.

Adverse Reactions Occurring at an Incidence of > 1% in Patients Treated With Bupropion Hydrochloride Immediate-release or Bupropion Hydrochloride Sustained-release Formulations in Major Depressive Disorder Trials

Table 3 summarizes the adverse reactions that occurred in placebo-controlled trials in patients treated with bupropion hydrochloride sustained-release at 300 mg/day and 400 mg/day. These include reactions that occurred in either the 300-mg/day or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group.

Table 3.	**Adverse Reactions in Placebo-controlled Trials for Major Depressive Disorder**		
Body System/Adverse Reaction	**Placebo (N = 385)**	**Bupropion Hydrochloride Sustained-release 300 mg/day (N = 376)**	**Bupropion Hydrochloride Sustained-release 400 mg/day (N = 114)**
Body (General)			
Headache	23%	26%	25%
Infection	6%	8%	9%
Abdominal pain	2%	3%	9%
Asthenia	2%	2%	4%
Chest pain	1%	3%	4%
Pain	2%	2%	3%
Fever	—	1%	2%
Cardiovascular			
Palpitation	2%	2%	6%
Flushing	—	1%	4%
Migraine	1%	1%	4%
Hot flashes	1%	1%	3%
Digestive			
Dry mouth	7%	17%	24%
Nausea	8%	13%	18%
Constipation	7%	10%	5%
Diarrhea	6%	5%	7%
Anorexia	2%	5%	3%
Vomiting	2%	4%	2%
Dysphagia	0%	0%	2%

Table 3.	**Adverse Reactions in Placebo-controlled Trials for Major Depressive Disorder**		
Body System/Adverse Reaction	**Placebo (N = 385)**	**Bupropion Hydrochloride Sustained-release 300 mg/day (N = 376)**	**Bupropion Hydrochloride Sustained-release 400 mg/day (N = 114)**
Musculoskeletal			
Myalgia	3%	2%	6%
Arthralgia	1%	1%	4%
Arthritis	0%	0%	2%
Twitch	—	1%	2%
Nervous System			
Insomnia	6%	11%	16%
Dizziness	5%	7%	11%
Agitation	2%	3%	9%
Anxiety	3%	5%	6%
Tremor	1%	6%	3%
Nervousness	3%	5%	3%
Somnolence	2%	2%	3%
Irritability	2%	3%	2%
Memory decreased	1%	—	3%
Paresthesia	1%	1%	2%
Central nervous system stimulation	1%	2%	1%
Respiratory			
Pharyngitis	2%	3%	11%
Sinusitis	2%	3%	1%
Increased cough	1%	1%	2%
Skin			
Sweating	2%	6%	5%
Rash	1%	5%	4%
Pruritus	2%	2%	4%
Urticaria	0%	2%	1%
Special Senses			
Tinnitus	2%	6%	6%
Taste perversion	—	2%	4%
Blurred vision or diplopia	2%	3%	2%

Table 3.	**Adverse Reactions in Placebo-controlled Trials for Major Depressive Disorder**		
Body System/Adverse Reaction	**Placebo (N = 385)**	**Bupropion Hydrochloride Sustained-release 300 mg/day (N = 376)**	**Bupropion Hydrochloride Sustained-release 400 mg/day (N = 114)**
Urogenital			
Urinary frequency	2%	2%	5%
Urinary urgency	0%	—	2%
Vaginal hemorrhage[a]	—	0%	2%
Urinary tract infection	—	1%	0%
[a] = Incidence based on the number of female patients.			
— = Denotes adverse reactions occurring in greater than 0 but less than 0.5% of patients.			

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

Changes in Body Weight

Table 4 presents the incidence of body weight changes (≥ 5 lbs) in the short-term MDD trials using bupropion hydrochloride sustained-release. There was a dose-related decrease in body weight.

Table 4.	**Incidence of Weight Gain or Weight Loss (≥ 5 lbs) in Placebo-controlled Trials of Bupropion Hydrochloride Sustained-release Tablets for Major Depressive Disorder**		
Weight Change	**Placebo (N = 347)**	**Bupropion Hydrochloride Sustained-release 300 mg/day (N = 339)**	**Bupropion Hydrochloride Sustained-release 400 mg/day (N = 112)**
Gained > 5 lbs	4%	3%	2%
Lost > 5 lbs	6%	14%	19%

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of bupropion hydrochloride. Because these reactions are reported voluntarily from a population of uncertain

size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body (General)—chills, facial edema, edema, peripheral edema, musculoskeletal chest pain, photosensitivity, and malaise.

Cardiovascular—postural hypotension, hypertension, stroke, vasodilation, syncope, complete atrioventricular block, extrasystoles, myocardial infarction, phlebitis, and pulmonary embolism.

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

Endocrine—hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone secretion.

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

Metabolic and Nutritional—glycosuria.

Musculoskeletal—leg cramps, fever/rhabdomyolysis, and muscle weakness.

Nervous System—abnormal coordination, depersonalization, emotional lability, hyperkinesia, hypertonia, hypesthesia, vertigo, amnesia, ataxia, derealization, abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hypokinesia, increased libido, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.

Respiratory—bronchospasm and pneumonia.

Skin—maculopapular rash, alopecia, angioedema, exfoliative dermatitis, and hirsutism.

Special Senses—accommodation abnormality, dry eye, deafness, increased intraocular pressure, angle-closure glaucoma, and mydriasis.

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

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect FORFIVO XL

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

Inhibitors of CYP2B6

Ticlopidine and Clopidogrel: Concomitant treatment with these drugs can increase bupropion exposures but decrease hydroxybupropion exposure. Coadministration of FORFIVO XL with ticlopidine or clopidogrel is not recommended [see *Clinical Pharmacology (12.3)*].

Inducers of CYP2B6

Ritonavir, Lopinavir, and Efavirenz: Concomitant treatment with these drugs can decrease bupropion and hydroxybupropion exposure. Patients receiving any of these drugs with bupropion may need increased doses of bupropion, but the maximum recommended dose of bupropion should not be exceeded [see *Clinical Pharmacology (12.3)*].

Carbamazepine, Phenobarbital, and Phenytoin: Although not systematically studied, these drugs may induce metabolism of bupropion and may decrease bupropion exposure [see *Clinical Pharmacology (12.3)*]. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion but the maximum recommended dose should not be exceeded.

7.2 Potential for FORFIVO XL to Affect Other Drugs

Drugs Metabolized by CYP2D6

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

Drugs that require metabolic activation by CYP2D6 to be effective (eg, tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with FORFIVO XL and such drugs may require increased doses of the drug [see *Clinical Pharmacology (12.3)*].

7.3 Drugs that Lower Seizure Threshold

Because there is no lower strength for FORFIVO XL, concurrent administration of FORFIVO XL tablets and agents that lower the seizure threshold (eg, other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids) should be undertaken only with extreme caution [see *Warnings and Precautions (5.3)*].

7.4 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was coadministered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Because there is no lower strength for FORFIVO XL, administration of FORFIVO XL tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

7.5 Use with Alcohol

In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. Alcohol increased the release rate of FORFIVO XL in vitro. The consumption of alcohol during treatment with FORFIVO XL should be avoided.

7.6 Monoamine Oxidase Inhibitors (MAOIs)

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAOI phenelzine. At least 14 days should elapse between discontinuation of an MAOI intended to treat depression and initiation of treatment with FORFIVO XL. Conversely, at least 14 days should be allowed after stopping FORFIVO XL before starting an MAOI antidepressant [see *Dosage and Administration (2.7, 2.8)* and *Contraindications (4)*].

7.7 Drug-Laboratory Test Interactions

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

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

Clinical Considerations

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

Human Data

Data from the international bupropion Pregnancy Registry (675 first-trimester exposures) and a retrospective cohort study using the United Healthcare database (1213 first-trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first-trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6853 infants with cardiovascular malformations and 5753 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

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

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

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

Animal Data

In studies conducted in rats and rabbits, bupropion was administered orally at doses of up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were observed at 50 mg/kg and greater. When rats were administered bupropion at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the approximately 6000 patients who participated in clinical trials with bupropion hydrochloride sustained-release tablets (depression and smoking cessation studies), 275 were ≥ 65 years of age and 47 were ≥ 75 years of age. In addition, several hundred patients ≥ 65 years of age participated in clinical trials using the immediate-release formulation of bupropion hydrochloride (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor

renal function [see *Dosage and Administration (2.6)*, *Use in Specific Populations (8.6)*, and *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Because there is no lower strength for FORFIVO XL, FORFIVO XL is not recommended in patients with renal impairment [see *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

Because there is no lower strength for FORFIVO XL, FORFIVO XL is not recommended in patients with hepatic impairment [see *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Bupropion is not a controlled substance.

9.2 Abuse

Humans

Controlled clinical studies of bupropion hydrochloride (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients demonstrated an increase in motor activity and agitation/excitement.

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

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

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

Animals

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

10 OVERDOSAGE

10.1 Human Overdose Experience

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

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

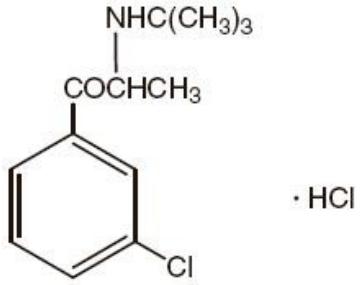
10.2 Overdosage Management

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

There are no known antidotes for bupropion. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Consider the possibility of multiple drug overdose.

11 DESCRIPTION

FORFIVO XL (bupropion hydrochloride), an antidepressant of the aminoketone class, is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitor, or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-2-(tert-Butylamino)-3'-chloropropiophenone hydrochloride. The molecular weight is 276.2. The empirical formula is $C_{13}H_{18}ClNO \cdot HCl$. Bupropion hydrochloride powder is white or almost white, crystalline, and soluble in water. It has a bitter taste and produces the sensation of local anesthesia on the oral mucosa. The structural formula is:



FORFIVO XL tablets are supplied for oral administration of 450 mg of bupropion hydrochloride as white to off-white extended-release tablets. Each film-coated tablet contains the labeled amount of bupropion hydrochloride and the inactive ingredients: hydroxypropyl cellulose, hydrochloric acid, polyvinyl pyrrolidone and polyvinyl acetate blend, polyethylene oxide, stearic acid, colloidal silicon dioxide, magnesium stearate, hydroxypropylmethyl cellulose, triacetin, talc, methacrylic acid copolymer, polyethylene glycol 8000, titanium dioxide and carboxymethyl cellulose sodium. The logo "Forfivo" is printed on one side of the tablet with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

Following single dosing under fasted conditions of FORFIVO XL tablets, the maximum peak plasma concentration (C_{max}), and the area under the plasma concentration versus time curve of bupropion from zero to infinity (AUC_{inf}), were 207.46 (± 59.40) ng/mL, and 2147.53 (± 664.12) ng·hr/mL, respectively. The elimination half-life (± SD) of bupropion after a single dose was 14.44 (± 5.00) hours.

In a single-dose study under fasting conditions, one FORFIVO XL tablet given once daily and three WELLBUTRIN XL 150 mg tablets once daily were evaluated. Equivalence was demonstrated for peak concentration and area under the curve for bupropion and the 3 metabolites (hydroxybupropion, erythrohydrobupropion, and threohydrobupropion).

Absorption

Following single oral administration of FORFIVO XL tablets to healthy volunteers, the median time to peak plasma concentrations for bupropion was approximately 5 hours under fasted conditions, and 12 hours under fed conditions. The presence of food did not affect the maximum peak plasma concentration for bupropion, however, mean systemic exposure to bupropion was

increased by 25% when FORFIVO XL tablets were taken with food. The food effect is not considered clinically significant and FORFIVO XL can be taken with or without food.

Distribution

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

Metabolism

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

In humans, peak plasma concentrations of hydroxybupropion occur approximately 10 hours after administration of a single dose of FORFIVO XL under fasted conditions and 16 hours under fed conditions. Following administration of WELLBUTRIN XL, peak plasma concentrations of hydroxybupropion are approximately 7 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (± 5) hours, and its AUC at steady state is about 13 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, the elimination half-lives of erythrohydrobupropion and threohydrobupropion are longer, approximately 33 (± 10) and 37 (± 13) hours, respectively, and steady-state AUCs are 1.4 and 7 times that of bupropion, respectively.

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

Elimination

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

Population Subgroups

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

Renal Impairment

There is limited information on the pharmacokinetics of bupropion in patients with renal impairment. An intertrial comparison between normal subjects and patients with end-stage renal failure demonstrated that the parent drug C_{max} and AUC values were comparable in the 2 groups, whereas the hydroxybupropion and threohydrobupropion metabolites had a 2.3- and 2.8-fold increase, respectively, in AUC for subjects with end-stage renal failure. A second study, comparing normal subjects and subjects with moderate to severe renal impairment (GFR 30.9 ± 10.8 mL/min) showed that after a single 150-mg dose of sustained-release bupropion, exposure to bupropion was approximately 2-fold higher in subjects with impaired renal function while levels of the hydroxybupropion and threo/erythrohydrobupropion (combined) metabolites were similar in the 2 groups. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. The elimination of the major metabolites of bupropion may be reduced by impaired renal function [see *Dosage and Administration (2.6)* and *Use in Specific Populations (8.6)*].

Hepatic Impairment

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

The second trial demonstrated no statistically significant differences in the pharmacokinetics of bupropion and its active metabolites in 9 subjects with mild to moderate hepatic cirrhosis compared to 8 healthy volunteers. However, more variability was observed in some of the pharmacokinetic parameters for bupropion (AUC, C_{max}, and T_{max}) and its active metabolites ($t_{½}$) in subjects with mild to moderate hepatic cirrhosis. In addition, in patients with severe hepatic cirrhosis, the bupropion C_{max} and AUC were substantially increased (mean difference: by approximately 70% and 3-fold, respectively) and more variable when compared to values in healthy volunteers; the mean bupropion half-life was also longer (29 hours in subjects with severe hepatic cirrhosis vs 19 hours in healthy subjects). For the metabolite hydroxybupropion, the mean C_{max} was approximately 69% lower. For the combined amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, the mean C_{max} was approximately 31% lower.

The mean AUC increased by about 1.5-fold for hydroxybupropion and about 2.5-fold for threo/erythrohydrobupropion. The median T_{max} was observed 19 hours later for hydroxybupropion and 31 hours later for threo/erythrohydrobupropion. The mean half-lives for hydroxybupropion and threo/erythrohydrobupropion were increased 5- and 2-fold, respectively, in patients with severe hepatic cirrhosis compared to healthy volunteers [see *Dosage and Administration (2.5)* and *Use in Specific Populations (8.7)*]**.**

Left Ventricular Dysfunction

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

Age

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

Gender

A single-dose study involving 12 healthy male and 12 healthy female volunteers revealed no sex-related differences in the pharmacokinetic parameters of bupropion. In addition, pooled analysis of bupropion pharmacokinetic data from 90 healthy male and 90 healthy female volunteers revealed no sex-related differences in the peak plasma concentrations of bupropion. The mean systemic exposure (AUC) was approximately 13% higher in male volunteers compared to female volunteers.

Smokers

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

Drug Interactions

Potential for Other Drugs to Affect FORFIVO XL

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

Inhibitors of CYP2B6

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

Prasugrel: In healthy subjects, prasugrel increased bupropion C_{max} and AUC values by 14% and 18%, respectively, and decreased C_{max} and AUC values of hydroxybupropion by 32% and 24%, respectively.

Cimetidine: Following oral administration of bupropion 300 mg with and without cimetidine 800 mg in 24 healthy young male volunteers, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion.

Citalopram: Citalopram did not affect the pharmacokinetics of bupropion and its 3 metabolites.

Inducers of CYP2B6

Ritonavir and Lopinavir: In a healthy volunteer study, ritonavir 100 mg twice daily reduced the AUC and C_{max} of bupropion by 22% and 21%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 23%, threohydrobupropion decreased by 38%, and erythrohydrobupropion decreased by 48%. In a second healthy volunteer study, ritonavir 600 mg twice daily decreased the AUC and the C_{max} of bupropion by 66% and 62%, respectively. The exposure of the hydroxybupropion metabolite was decreased by 78%, threohydrobupropion decreased by 50%, and erythrohydrobupropion decreased by 68%.

In another healthy volunteer study, lopinavir 400 mg/ritonavir 100 mg twice daily decreased bupropion AUC and C_{max} by 57%. The AUC and C_{max} of the hydroxybupropion metabolite were decreased by 50% and 31%, respectively.

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

Carbamazepine, Phenobarbital, Phenytoin: Although not systematically studied, these drugs may induce the metabolism of bupropion.

Potential for FORFIVO XL to Affect Other Drugs

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

Drugs Metabolized by CYP2D6

In vitro, bupropion and hydroxybupropion are CYP2D6 inhibitors. In a clinical study of 15 male subjects (19 to 35 years of age) who were extensive metabolizers of CYP2D6, bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{½}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in one Ames bacterial mutagenicity assay, but was negative in another. Bupropion produced an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies.

A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility.

14 CLINICAL STUDIES

The efficacy of bupropion in the treatment of MDD was established with the immediate-release formulation of bupropion hydrochloride in two 4-week, placebo-controlled trials in adult inpatients with MDD and in one 6-week, placebo-controlled trial in adult outpatients with MDD. In the first study, the bupropion dose range was 300 to 600 mg/day administered in 3 divided

doses; 78% of patients were treated with doses of 300 to 450 mg/day. The trial demonstrated the efficacy of bupropion as measured by the Hamilton Depression Rating Scale (HDRS) total score, the HDRS depressed mood item (item 1), and the Clinical Global Impressions-Severity Scale (CGI-S). The second study included 2 fixed doses of bupropion (300 and 450 mg/day) and placebo. This trial demonstrated the efficacy of bupropion for only the 450-mg dose. The efficacy results were significant for the HDRS total score and the CGI-S score, but not for HDRS item 1. In the third study, outpatients were treated with bupropion at 300 mg/day. This study demonstrated the efficacy of bupropion as measured by the HDRS total score, the HDRS item 1, the Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S score, and the CGI-Improvement Scale (CGI-I) score.

A longer-term, placebo-controlled, randomized withdrawal trial demonstrated the efficacy of bupropion hydrochloride sustained-release in the maintenance treatment of MDD. The trial included adult outpatients meeting DSM-IV criteria for MDD, recurrent type, who had responded during an 8-week open-label trial of bupropion 300 mg/day. Responders were randomized to continuation of bupropion at 300 mg/day or placebo, for up to 44 weeks of observation for relapse. Response during the open-label phase was defined as a CGI-I score of 1 (very much improved) or 2 (much improved) for each of the final 3 weeks. Relapse during the double-blind phase was defined as the investigator's judgment that drug treatment was needed for worsening depressive symptoms. Patients in the bupropion group experienced significantly lower relapse rates over the subsequent 44 weeks compared to those in the placebo group.

Although there are no independent trials demonstrating the efficacy of bupropion extended-release in the acute treatment of MDD, studies have demonstrated similar bioavailability between the immediate-, sustained-, and extended-release formulations of bupropion hydrochloride under steady-state conditions (ie, the exposures [C_{max} and AUC] for bupropion and its metabolites are similar among the 3 formulations). Further, it has been demonstrated that FORFIVO XL is bioequivalent to WELLBUTRIN XL.

16 HOW SUPPLIED/STORAGE AND HANDLING

FORFIVO XL Extended-Release Tablets, 450 mg of bupropion hydrochloride, are white to off-white, oblong-shaped tablets printed with the "Forfivo" logo on one side supplied in bottles of 30 tablets (NDC 49909-010-30).

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients, their families, and their caregivers about the benefits and risks associated with treatment with FORFIVO XL and counsel them in its appropriate use.

A patient Medication Guide about "Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions", "Quitting Smoking, Quit-smoking Medications, Changes in Thinking and Behavior, Depression, and Suicidal Thoughts or Actions"

and "What Other Important Information Should I Know about FORFIVO XL" is available for FORFIVO XL. Instruct patients, their families, and their caregivers to read the Medication Guide and assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Advise patients regarding the following issues and to alert their prescriber if these occur while taking FORFIVO XL.

Suicidal Thoughts and Behaviors

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

Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

Although FORFIVO XL is not indicated for smoking cessation treatment, it contains the same active ingredient as ZYBAN® which is approved for this use. Advise patients, families, and caregivers that quitting smoking, with or without ZYBAN, may trigger nicotine withdrawal symptoms (eg, including depression or agitation), or worsen pre-existing psychiatric illness. Some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide when attempting to quit smoking while taking ZYBAN. If patients develop agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to report these symptoms to their healthcare provider immediately.

Severe Allergic Reactions

Educate patients on the symptoms of hypersensitivity and to discontinue FORFIVO XL if they have a severe allergic reaction.

Seizure

Instruct patients to discontinue and not restart FORFIVO XL if they experience a seizure while on treatment. Advise patients that the excessive use or the abrupt discontinuation of alcohol, benzodiazepines, antiepileptic drugs, or sedatives/hypnotics can increase the risk of seizure. Advise patients to avoid the use of alcohol.

Angle-closure Glaucoma

Patients should be advised that taking FORFIVO XL can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle-closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle-closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle-closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (eg, iridectomy), if they are susceptible [see *Warnings and Precautions (5.7)*].

Bupropion-containing Products

Educate patients that FORFIVO XL contains the same active ingredient (bupropion) found in ZYBAN, which is used as an aid to smoking cessation treatment, and that FORFIVO XL should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as WELLBUTRIN XL, the extended-release formulation; WELLBUTRIN SR®, the sustained-release formulation; WELLBUTRIN®, the immediate-release formulation; and APLENZIN®, a bupropion hydrobromide formulation). In addition, there are a number of generic bupropion hydrochloride products for the immediate-, sustained-, and extended-release formulations.

Potential for Cognitive and Motor Impairment

Advise patients that any CNS-active drug like FORFIVO XL tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Advise patients that until they are reasonably certain that FORFIVO XL tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. FORFIVO XL treatment may lead to decreased alcohol tolerance.

Concomitant Medications

Counsel patients to notify their healthcare provider if they are taking or plan to take any prescription or over-the-counter drugs, because FORFIVO XL tablets and other drugs may affect each other's metabolism.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy.

Precautions for Nursing Mothers

Communicate with the patient and pediatric healthcare provider regarding the infant's exposure to bupropion through human milk. Instruct patients to immediately contact the infant's healthcare provider if they note any side effect in the infant that concerns them or is persistent.

Administration Information

Instruct patients to swallow FORFIVO XL tablets whole so that the release rate is not altered. Instruct patients that FORFIVO XL tablets should not be chewed, divided, or crushed. FORFIVO XL may be taken with or without food.

Manufactured by:
Pillar5 Pharma, Inc.
Arnprior, Ontario, K7S 0C9
Canada

For:
Edgemont Pharmaceuticals, LLC
Austin, TX 78746

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