BUPROPION HYDROCHLORIDE XL- bupropion hydrochloride tablet, extended release

Slate Run Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLETS (XL) safely and effectively. See full prescribing information for BUPROPION HYDROCHLORIDE EXTENDED-RELEASE TABLETS (XL).

BUPROPION HYDROCHLORIDE extended-release tablets (XL) for oral use

Initial U.S. Approval: 1985

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
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)**

INDICATIONS AND USAGE

Bupropion hydrochloride extended-release tablets (XL) are an aminoketone antidepressant, indicated for:
• treatment of major de pressive disorder (MDD) (1.1)
• prevention of seasonal affective disorder (SAD) (1.2)

DOSAGE AND ADMINISTRATION

General:
- Increase dose gradually to reduce seizure risk. (2.1, 5.3)
- Periodically reassess the dose and need for maintenance treatment. (2.2)

Major Depressive Disorder
- Starting dose: 150 mg once daily. Usual target dose: 300 mg once daily (2.2)
- After 4 days, may increase the dose to 300 mg once daily. (2.2)

Seasonal Affective Disorder
- Initiate treatment in the autumn prior to onset of seasonal depressive symptoms. (2.3)
- Starting dose: 150 mg once daily. Usual target dose: 300 mg once daily. (2.3)
- After one week, may increase the dose to 300 mg once daily. (2.3)
- Continue treatment through the winter season. (2.3)

Hepatic Impairment
- Moderate to severe hepatic impairment: 150 mg every other day (2.6)
- Mild hepatic impairment: Consider reducing the dose and/or frequency of dosing. (2.6, 8.7)

Renal Impairment
- Consider reducing the dose and/or frequency of dosing. (2.7, 8.6)

DOSAGE FORMS AND STRENGTHS

- Extended-release tablets: 150 mg, 300 mg (3)

CONTRAINDICATIONS

- Seizure disorder. (4, 5.3)
- Current or prior diagnosis of bulimia or anorexia nervosa (4, 5.3)
- Abrupt discontinuation of alcohol, benzodiazepines, barbiturates, antiepileptic drugs. (4, 5.3)
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with

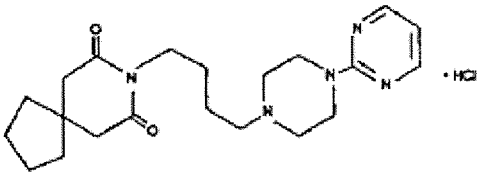
BUSPIRONE HYDROCHLORIDE- buspirone hydrochloride tablet
EPIC PHARMA, LLC

BUSPIRONE HYDROCHLORIDE TABLETS, USP
(Patient Instruction Sheet Included)
Rx only

DESCRIPTION

Buspirone hydrochloride tablets, USP is an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.

Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, buspirone hydrochloride is *N*-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride, which can be represented by the following tructural formula:



$C_{21}H_{31}N_5O_2 \cdot HCl$ M.W. 422.0

Each tablet for oral administration contains 5 mg, 10 mg, 15 mg, or 30 mg of buspirone hydrochloride, USP (equivalent to 4.6 mg, 9.1 mg, 13.7 mg, and 27.4 mg of buspirone free base, respectively). The 5 mg and 10 mg tablets are scored so they can be bisected. Thus, the 5 mg tablet can also provide a 2.5 mg dose, and the 10 mg tablet can provide a 5 mg dose. The 15 mg tablets are scored so they can be either bisected or trisected. Thus, a single 15 mg tablet can provide the following doses: 15 mg (entire tablet), 10 mg (two thirds of a tablet), 7.5 mg (one half of a tablet), or 5 mg (one third of a tablet). A single 30 mg tablet can provide the following doses: 30 mg (entire tablet), 20 mg (two thirds of a tablet), 15 mg (one half of a tablet), or 10 mg (one third of a tablet). Buspirone hydrochloride tablets USP contain the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

The mechanism of action of buspirone is unknown. Buspirone differs from typical benzodiazepine anxiolytics in that it does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. *In vitro* preclinical studies have shown that buspirone has a high affinity for serotonin (5-HT_{1A}) receptors. Buspirone has no significant affinity for benzodiazepine receptors and does not affect GABA binding *in vitro* or *in vivo* when tested in preclinical models.

Buspirone has moderate affinity for brain D_2-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

Buspirone is rapidly absorbed in man and undergoes extensive first-pass metabolism. In a radiolabeled study, unchanged buspirone in the plasma accounted for only about 1% of the radioactivity in the plasma. Following oral administration, plasma concentrations of unchanged buspirone are very low and variable between subjects. Peak plasma levels of 1 ng/mL to 6 ng/mL have been observed 40 to 90 minutes after single oral doses of 20 mg. The single-dose bioavailability of unchanged buspirone when taken as a tablet is on the average about 90% of an equivalent dose of solution, but there is large variability.

The effects of food upon the bioavailability of buspirone hydrochloride tablets have been studied in

The efficacy of buspirone hydrochloride tablets has been demonstrated in controlled clinical trials of outpatients whose diagnosis roughly corresponds to Generalized Anxiety Disorder (GAD). Many of the patients enrolled in these studies also had coexisting depressive symptoms and buspirone hydrochloride tablets relieved anxiety in the presence of these coexisting depressive symptoms. The patients evaluated in these studies had experienced symptoms for periods of 1 month to over 1 year prior to the study, with an average symptom duration of 6 months. Generalized Anxiety Disorder (300.02) is described in the American Psychiatric Association's Diagnostic and Statistical Manual, III[1] as follows:

Generalized, persistent anxiety (of at least 1 month continual duration), manifested by symptoms from three of the four following categories:

1. Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

2. Autonomic hyperactivity: sweating, heart pounding or racing, cold, clammy hands, dry mouth, dizziness, lightheadedness, paresthesias (tingling in hands or feet), upset stomach, hot or cold spells, frequent urination, diarrhea, discomfort in the pit of the stomach, lump in the throat, flushing, pallor, high resting pulse and respiration rate.

3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.

4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling "on edge," irritability, impatience.

The above symptoms would not be due to another mental disorder, such as a depressive disorder or schizophrenia. However, mild depressive symptoms are common in GAD.

The effectiveness of buspirone hydrochloride tablets in long-term use, that is, for more than 3 to 4 weeks, has not been demonstrated in controlled trials. There is no body of evidence available that systematically addresses the appropriate duration of treatment for GAD. However, in a study of long-term use, 264 patients were treated with buspirone hydrochloride tablets for 1 year without ill effect. Therefore, the physician who elects to use buspirone hydrochloride tablets for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Buspirone hydrochloride tablets are contraindicated in patients hypersensitive to buspirone hydrochloride.

The use of monoamine oxidase inhibitors (MAOIs) intended to treat depression with buspirone or within 14 days of stopping treatment with buspirone is contraindicated because of an increased risk of serotonin syndrome and/or elevated blood pressure. The use of buspirone within 14 days of stopping an MAOI intended to treat depression is also contraindicated.

Starting buspirone in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome. (see **WARNINGS**, **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS: Drug Interactions**)

WARNINGS

The administration of buspirone hydrochloride tablets to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when buspirone hydrochloride has been added to a regimen including an MAOI. Therefore, it is recommended that buspirone hydrochloride tablets not be used concomitantly with an MAOI.

Serotonin Syndrome

time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible Concerns Related to Buspirone's Binding to Dopamine Receptors

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine-mediated neurological function (e.g., dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). See **ADVERSE REACTIONS: Postmarketing Experience**.

Information for Patients

To assure safe and effective use of buspirone hydrochloride tablets, the following information and instructions should be given to patients:
1. Do not take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
2. Do not take an MAOI within 2 weeks of stopping buspirone unless directed to do so by your physician.
3. Do not start buspirone if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
4. Inform your physician about any medications, prescription or non-prescription, alcohol, or drugs that you are now taking or plan to take during your treatment with buspirone hydrochloride tablets.
5. Inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking buspirone hydrochloride tablets.
6. Inform your physician if you are breast-feeding an infant.
7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.
8. You should take buspirone hydrochloride tablets consistently, either always with or always without food.
9. During your treatment with buspirone hydrochloride tablets, avoid drinking large amounts of grapefruit juice.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Psychotropic Agents

MAO inhibitors: The use of monoamine oxidase inhibitors (MAOIs) intended to treat depression with buspirone or within 14 days of stopping treatment with buspirone is contraindicated because of an increased risk of serotonin syndrome and/or elevated blood pressure. The use of buspirone within 14 days of stopping an MAOI intended to treat depression is also contraindicated.

Starting buspirone in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome. (see **CONTRAINDICATIONS, WARNINGS**, and **DOSAGE AND ADMINISTRATION**).

Amitriptyline: After addition of buspirone to the amitriptyline dose regimen, no statistically significant

significant decreases (about 50%) in plasma concentrations of the buspirone metabolite 1-PP. With 5 mg b.i.d. doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (HO-NEF) (17%) and meta-chlorophenylpiperazine (9%). Slight increases in C_{max} were observed for nefazodone (8%) and its metabolite HO-NEF (11%). Subjects receiving buspirone 5 mg b.i.d. and nefazodone 250 mg b.i.d experienced lightheadedness, asthenia, dizziness, and somnolence, adverse events also observed with either drug alone. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Rifampin: In a study in healthy volunteers, coadministration of buspirone (30 mg as a single dose) with rifampin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in C_{max}; 89.6% decrease in AUC) and pharmacodynamic effects of buspirone. If the two drugs are to be used in combination, the dosage of buspirone may need adjusting to maintain anxiolytic effect.

Other Inhibitors and Inducers of CYP3A4: Substances that inhibit CYP3A4, such as ketoconazole or ritonavir, may inhibit buspirone metabolism and increase plasma concentrations of buspirone while substances that induce CYP3A4, such as dexamethasone or certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase the rate of buspirone metabolism. If a patient has been titrated to a stable dosage on buspirone, a dose adjustment of buspirone may be necessary to avoid adverse events attributable to buspirone or diminished anxiolytic activity. Consequently, when administered with a potent inhibitor of CYP3A4, a low dose of buspirone used cautiously is recommended. When used in combination with a potent inducer of CYP3A4 the dosage of buspirone may need adjusting to maintain anxiolytic effect.

Other Drugs

Cimetidine: Coadministration of buspirone with cimetidine was found to increase C_{max} (40%) and T_{max} (2-fold), but had minimal effects on the AUC of buspirone.

Protein Binding

In vitro, buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins. However, there has been one report of prolonged prothrombin time when buspirone was added to the regimen of a patient treated with warfarin. The patient was also chronically receiving phenytoin, phenobarbital, digoxin, and Synthroid®. *In vitro*, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.

Therapeutic levels of aspirin, desipramine, diazepam, flurazepam, ibuprofen, propranolol, thioridazine, and tolbutamide had only a limited effect on the extent of binding of buspirone to plasma proteins (see **CLINICAL PHARMACOLOGY**).

Drug/Laboratory Test Interactions

Buspirone hydrochloride may interfere with the urinary metanephrine/catecholamine assay. It has been mistakenly read as metanephrine during routine assay testing for pheochromocytoma, resulting in a false positive laboratory result. Buspirone hydrochloride should therefore be discontinued for at least 48 hours prior to undergoing a urine collection for catecholamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed in rats during a 24-month study at approximately 133 times the maximum recommended human oral dose; or in mice, during an 18-month study at approximately 167 times the maximum recommended human oral dose.

With or without metabolic activation, buspirone did not induce point mutations in five strains of *Salmonella typhimurium* (Ames Test) or mouse lymphoma L5178YTK+ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.

One guide to the relative clinical importance of adverse events associated with buspirone hydrochloride tablets is provided by the frequency with which they caused drug discontinuation during clinical testing. Approximately 10% of the 2200 anxious patients who participated in the buspirone hydrochloride tablets premarketing clinical efficacy trials in anxiety disorders lasting 3 to 4 weeks discontinued treatment due to an adverse event. The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, and lightheaded feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials

The table that follows enumerates adverse events that occurred at a frequency of 1% or more among buspirone hydrochloride patients who participated in 4-week, controlled trials comparing buspirone hydrochloride tablets with placebo. The frequencies were obtained from pooled data for 17 trials. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. Comparison of the cited figures, however, does provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS*
(Percent of Patients Reporting)

Adverse Experience	Buspirone (n=477)	Placebo (n=464)
Cardiovascular		
Tachycardia/Palpitations	1	1
CNS		
Dizziness	12	3
Drowsiness	10	9
Nervousness	5	1
Insomnia	3	3
Lightheadedness	3	---
Decreased Concentration	2	2
Excitement	2	---
Anger/Hostility	2	---
Confusion	2	---
Depression	2	2
EENT		
Blurred Vision	2	---
Gastrointestinal		
Nausea	8	5
Dry Mouth	3	4
Abdominal/Gastric Distress	2	2
Diarrhea	2	---
Constipation	1	2
Vomiting	1	2
Musculoskeletal		
Musculoskeletal Aches/Pains	1	---

Rare were galactorrhea and thyroid abnormality.

Gastrointestinal

Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon, and rectal bleeding; rare was burning of the tongue.

Genitourinary

Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis, and nocturia.

Musculoskeletal

Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias; rare was muscle weakness.

Respiratory

Infrequent were hyperventilation, shortness of breath, and chest congestion; rare was epistaxis.

Sexual Function

Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.

Skin

Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, and blisters; rare were acne and thinning of nails.

Clinical Laboratory

Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia, and thrombocytopenia.

Miscellaneous

Infrequent were weight gain, fever, roaring sensation in the head, weight loss, and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice, and hiccoughs.

Postmarketing Experience

Postmarketing experience has shown an adverse experience profile similar to that given above. Voluntary reports since introduction have included rare occurrences of allergic reactions (including urticaria), angioedema, cogwheel rigidity, dizziness (rarely reported as vertigo), dystonic reactions (including dystonia), ataxias, extrapyramidal symptoms, dyskinesias (acute and tardive), ecchymosis, emotional lability, serotonin syndrome, transient difficulty with recall, urinary retention, visual changes (including tunnel vision), parkinsonism, akathisia, restless leg syndrome, and restlessness. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to buspirone hydrochloride tablets treatment has not been determined.

To report SUSPECTED ADVERSE REACTIONS, contact Epic Pharma at 1-888-374-2791, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Buspirone hydrochloride is not a controlled substance.

Physical and Psychological Dependence

In human and animal studies, buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. Human volunteers

Methylene Blue

Do not start buspirone hydrochloride tablets in a patient who is being treated with a reversible MAOI such as linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, non-pharmacological interventions, including hospitalization, should be considered (see **CONTRAINDICATIONS** and **PRECAUTIONS: Drug Interactions**).

In some cases, a patient already receiving therapy with buspirone hydrochloride tablets 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 serotonin syndrome in a particular patient, buspirone hydrochloride tablets should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with buspirone hydrochloride tablets may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see **WARNINGS**).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg per kg with buspirone hydrochloride tablets is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see **CONTRAINDICATIONS**, **WARNINGS** and **PRECAUTIONS: Drug Interactions**).

HOW SUPPLIED

Buspirone Hydrochloride Tablets, USP 5 mg are available as white, or almost white, oval tablets debossed with the code Y1 on one side and a score on the other side. They are packaged as follows:

Bottles of 100 (packaged in a single bottle) NDC 42806-662-01
Bottles of 500 (packaged in a single bottle) NDC 42806-662-05

Buspirone Hydrochloride Tablets, USP 10 mg are available as white, or almost white, oval tablets debossed with the code Y7 on one side and a score on the other side. They are packaged as follows:

Bottles of 100 (packaged in a single bottle) NDC 42806-663-01
Bottles of 500 (packaged in a single bottle) NDC 42806-663-05

Buspirone Hydrochloride Tablets, USP 15 mg are available as white, or almost white, bar-shaped tablets debossed with the code Y53 on one side and a score on one side and two scores on the other side. They are packaged as follows:

Bottles of 100 (packaged in a single bottle) NDC 42806-664-01
Bottles of 500 (packaged in a single bottle) NDC 42806-664-05

Buspirone Hydrochloride Tablets, USP 30 mg are available as white, or almost white, bar-shaped tablets debossed with the code Y54 on one side and two scores on the other side. They are packaged as follows:

Bottles of 60 (packaged in a single bottle) NDC 42806-665-60

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

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

REFERENCE