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August 16, 2023

Dockets Management

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

LABELING AMENDMENT

**Reference: Buspirone Hydrochloride Tablets USP, 2.5 mg, 3.75 mg, and 12.5 mg
Amendment of Labeling
Suitability Petition FDA-2022-P-1039**

Dear Sir or Madam:

Reference is made to Epic Pharma, LLC proposed suitability petition, FDA-2022-P-1039, seeking permission to file an ANDA for Buspirone Hydrochloride Tablets USP, 2.5 mg, 3.75 mg, and 12.5 mg, submitted on June 7, 2022.

Reference is also made to the Agency's Information Request Email dated August 8, 2023. The Agency's comment is provided below in bold and followed by Epic Pharma, LLC's response.

1. Pursuant to 21 CFR 314.93(d), provide the proposed drug product labeling.

Response:

Epic Pharma LLC acknowledges above the comment from the Agency and has provided proposed drug product labeling. In support of this amendment, the following labeling components have been included the attachments:

- **[Attachment 1 Agency's Information Request Email](#)**
- **[Attachment 2 Epic Proposed labeling Rev.08-2023](#)**
- **[Attachment 3 Reference Listed Drug, BuSpar Tablets Model Labeling Provided by FDA](#)**
- **[Attachment 4 FDA Email of Providing BuSpar Tablets Model Labeling](#)**
- **[Attachment 5 Side-by-Side Comparison Proposed vs Current Approved vs RLD Labeling](#)**

Please do not hesitate to contact me for any additional information by phone (347) 238-2729, or email at RADept@epic-pharma.com.

Sincerely,

Mr. Pei Zhang Ph.D.
Associate Director of Regulatory Affairs
Epic Pharma, LLC

RA Dept

From: Nguyen, Kim-Yen <Kim-Yen.Nguyen@fda.hhs.gov>
Sent: Tuesday, August 8, 2023 10:55 AM
To: RA Dept
Cc: ANDAFiling
Subject: Suitability Petition (FDA-2022-P-1039) Information Request

WARNING!! This message comes from an external organization. Be careful of embedded links.

Docket No. FDA-2022-P-1039

Dear Xiaofeng Meng:

Reference is made to your suitability petition FDA-2022-P-1039, received on June 7, 2022, seeking permission to file an ANDA for Bupirone Hydrochloride Tablets USP, 2.5 mg, 3.75 mg, and 12.5 mg. We ask that you submit the following information as an amendment to the aforementioned petition to the Division of Dockets Management, in order for the Agency to complete the review of this petition:

1. Pursuant to 21 CFR 314.93(d), provide the proposed drug product labeling.

Your response should reference the docket number for the petition and be sent to the following address or submitted electronically at <https://link.edgepilot.com/s/e371bc99/6Z4V4-Exuk61oZWdSKP0lg?u=http://www.regulations.gov/>:

Dockets Management

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

We request that you acknowledge receipt of this correspondence. Please provide a complete response to all of the items identified above within 30 calendar-days from the date of this communication. In addition, please notify me via email or telephone when you have submitted your response with a cc to: ANDAFiling@fda.hhs.gov.

It is important to note the Agency and industry agreed to certain commitments related to Suitability Petitions as part of the reauthorization of the Generic Drug User Fee Amendments and as described in "GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2023- 2027" (GDUFA III commitment letter)^[1]. We note that, in accordance with the GDUFA III commitment letter FDA agreed to certain goals and procedures for the review of suitability petitions. FDA agreed to take appropriate action prior to FY 2024 to determine if petitioners who submitted suitability petitions prior to FY 2023 remain interested in a response. FDA also agreed that any suitability petition submitted in FY 2024-2027 will receive a goal date. More details about these goal dates are included in the GDUFA III commitment letter. Any suitability petitions submitted to FDA prior to FY 2024 will not receive a goal date. If a petitioner wants to receive a goal date on a suitability petition submitted prior to FY 2024, the petitioner may withdraw and submit a new suitability petition in FY 2024-2027.

In light of this commitment, you may want to consider withdrawing and resubmitting your suitability petition. In order to receive a goal date for a resubmitted petition, you must not resubmit before October 1, 2023; however, you do not need to wait until October 1, 2023 to withdraw your petition. In addition, if you no longer require an

answer, you may also withdraw your petition. Instructions for how to withdraw and resubmit your petition are below.

To withdraw your petition, please submit a letter stating that you are withdrawing your petition. You should submit the letter electronically to the petition docket at <https://link.edgepilot.com/s/e371bc99/6Z4V4-Exuk61oZWdSKP0lg?u=http://www.regulations.gov/> (search for your petition docket number to find your petition. Then select Comment Now to upload your letter).

Suitability petitions are a type of Citizen Petition and are submitted through the Division of Dockets Management.

MAPP 5240.5 Rev. 2 entitled ANDA Suitability Petitions is publicly available. It provides additional information about the suitability petition process.

For questions regarding submitting a suitability petition, contact the FDA Office of Generic Drugs: GenericDrugs@fda.hhs.gov

For questions specifically regarding this Information Request, please contact me at Kim-Yen.Nguyen@fda.hhs.gov or by phone at 240-402-8869.

Best Regards,
Kim Nguyen

Kim-Yen [Kim] Nguyen

Project Manager, OGD/ORO/DFR

Center for Drug Evaluation and Research
Office of Generic Drugs
U.S. Food and Drug Administration
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^[1] The GDUFA III Commitment Letter is available at: <https://link.edgepilot.com/s/472f7a04/QixleyiUEUioBLP60SLzow?u=https://www.fda.gov/media/153631/download>

Epic Pharma, LLC Proposed Drug Product Labeling - Rev. 08-2023-00

Buspirone Hydrochloride Tablets, USP

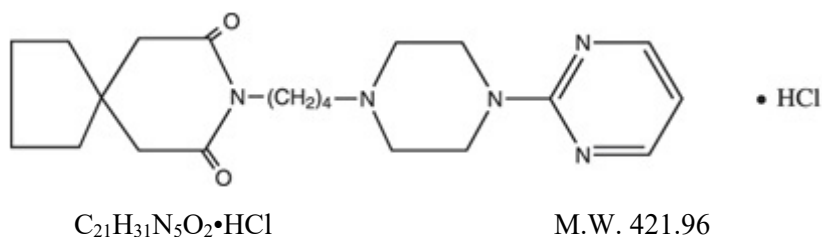
Rx Only

(Patient Instruction Sheet Included)

DESCRIPTION

Buspirone hydrochloride tablets, USP are 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 421.96. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione monohydrochloride. The empirical formula $C_{21}H_{31}N_5O_2 \cdot HCl$ is represented by the following structural formula:



Each tablet, for oral administration, contains 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg or 30 mg of buspirone hydrochloride, USP (equivalent to 2.3 mg, 3.4 mg, 4.6 mg, 6.9 mg, 9.1 mg, 11.4 mg, 13.7 mg and 27.4 mg of buspirone free base, respectively). The 2.5 mg, 3.75 mg, 12.5 mg tablets are unscored. 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 and 30 mg tablets are cored 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: anhydrous lactose, colloidal silicon dioxide, 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 D₂-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

Buspirone hydrochloride 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 eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see **DOSAGE AND ADMINISTRATION**).

A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single-dose studies.

An *in vitro* protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone *in vivo*, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An *in vitro* study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.

Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by cytochrome P450 3A4 (CYP3A4) (see **PRECAUTIONS, Drug Interactions**). Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to buspirone hydrochloride do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/mL, less than 1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.

In a single-dose study using ^{14}C -labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 mg to 40 mg is about 2 to 3 hours.

Special Populations

Age and Gender Effects

After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C_{\max}) were observed between elderly and younger subjects or between men and women.

Hepatic Impairment

After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see **PRECAUTIONS**).

Renal Impairment

After multiple-dose administration of buspirone to renally impaired ($Cl_{cr}=10-70$ mL/min/1.73 m²) patients, steady-state AUC of buspirone increased 4-fold compared with healthy ($Cl_{cr}\geq 80$ mL/min/1.73 m²) subjects (see **PRECAUTIONS**).

Race Effects

The effects of race on the pharmacokinetics of buspirone have not been studied.

INDICATIONS AND USAGE

Buspirone hydrochloride tablets are indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

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, III¹ 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 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 not be used concomitantly with an MAOI.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs, SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (in particular, MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus,

hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for emergence of serotonin syndrome.

The concomitant use of buspirone with MAOIs intended to treat depression is contraindicated. Buspirone should also not be started in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. There have been no reports involving the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a reversible MAOI such as linezolid or intravenous methylene blue in a patient taking buspirone. Buspirone should be discontinued before initiating treatment with the reversible MAOI [see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS**].

If concomitant use of buspirone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of buspirone with serotonin precursors (such as tryptophan) is not recommended.

Treatment with buspirone and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Because buspirone hydrochloride tablets have no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS

General

Interference with Cognitive and Motor Performance

Studies indicate that buspirone is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of buspirone hydrochloride with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients

Because buspirone does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone hydrochloride tablets, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying 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 **WARNINGS, DOSAGE AND ADMINISTRATION AND CONCOMITANT DRUG**)

Amitriptyline: After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) of amitriptyline or its metabolite nortriptyline were observed.

Diazepam: After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

Haloperidol: In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.

Nefazodone: (see **Inhibitors and Inducers of Cytochrome P450 3A4 [CYP3A4]**)

Trazodone: There is one report suggesting that the concomitant use of Desyrel® (trazodone hydrochloride) and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

Triazolam/Flurazepam: Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.

Other Psychotropics: Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.

Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)

Buspirone has been shown *in vitro* to be metabolized by CYP3A4. This finding is consistent with the *in vivo* interactions observed between buspirone and the following:

Diltiazem and Verapamil: In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased AUC and C_{max} of buspirone 3.4-fold while diltiazem increased AUC and C_{max} 5.5-fold and 4-fold, respectively). Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.

Erythromycin: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C_{max} and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Grapefruit juice: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C_{max} ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.

Itraconazole: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C_{max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. 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.

Nefazodone: In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically 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.

Pregnancy

Teratogenic Effects

Pregnancy Category B

No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have *not* been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of buspirone hydrochloride on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

Nursing Mothers

The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. Buspirone hydrochloride administration to nursing women should be avoided if clinically possible.

Pediatric Use

The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6-week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses studied were 7.5 mg to 30 mg b.i.d. (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.

Geriatric Use

In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

There were no effects of age on the pharmacokinetics of buspirone (see **CLINICAL PHARMACOLOGY: Special Populations**).

Use in Patients With Impaired Hepatic or Renal Function

Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a lengthened half-life of buspirone. Therefore, the administration of buspirone hydrochloride tablets to patients with severe hepatic or renal impairment cannot be recommended (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS (See also PRECAUTIONS.)

Commonly Observed

The more commonly observed untoward events associated with the use of buspirone hydrochloride tablets not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment

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 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)

	Buspirone Hydrochloride Tablets (n=477)	Placebo (n=464)
Adverse Experience		
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	-
Neurological		
Numbness	2	-
Paresthesia	1	-
Incoordination	1	-
Tremor	1	-
Skin		
Skin Rash	1	-
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	-
Sweating/Clamminess	1	-

* Events reported by at least 1% of buspirone hydrochloride tablets patients are included.

- Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of Buspirone Hydrochloride Tablets

During its premarketing assessment, buspirone hydrochloride was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of buspirone hydrochloride in the dose range for which buspirone is being recommended (i.e., the modal daily dose of buspirone hydrochloride fell between 10 mg and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone hydrochloride varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to buspirone hydrochloride treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the **PRECAUTIONS** section.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular

Frequent was nonspecific chest pain; infrequent were syncope, hypotension, and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.

Central Nervous System

Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.

EENT

Frequent were tinnitus, sore throat, and nasal congestion; infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.

Endocrine

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 with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between buspirone hydrochloride tablets and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that buspirone hydrochloride tablets cause physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS-active drug will be

misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone hydrochloride tablets misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Signs and Symptoms

In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with buspirone hydrochloride tablets alone. Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD₅₀ values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 550 times the recommended human daily dose.

Recommended Overdose Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.

DOSAGE AND ADMINISTRATION

The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 mg to 30 mg per day were commonly employed.

The bioavailability of buspirone is increased when given with food as compared to the fasted state (see **CLINICAL PHARMACOLOGY**). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.

When buspirone is to be given with a potent inhibitor of CYP3A4, the dosage recommendations described in the **PRECAUTIONS, Drug Interactions** section should be followed.

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 buspirone hydrochloride tablets. Conversely, at least 14 days should be allowed after stopping buspirone hydrochloride tablets before starting an MAOI antidepressant (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**).

Use of Buspirone Hydrochloride Tablets with (Reversible) MAOIs, Such as Linezolid or 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 **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 **DRUG INTERACTIONS**).

HOW SUPPLIED

Buspirone Hydrochloride Tablets USP, 2.5 mg are available as white to off-white, round, unscored tablets, debossed "C" above "78" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.

NDC 42806-078-01 Bottles of 100 Tablets

NDC 42806-078-05 Bottles of 500 Tablets

Buspirone Hydrochloride Tablets USP, 3.75 mg are available as white to off-white, round, unscored tablets, debossed "C" above "79" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.

NDC 42806-079-01 Bottles of 100 Tablets

NDC 42806-079-05 Bottles of 500 Tablets

Buspirone Hydrochloride Tablets USP, 5 mg are available as white to off-white, round, beveled-edge tablets, scored on one side and debossed "C" above "82" on the other side, and packaged in bottles of 100 and 500 tablets.

NDC 42806-082-01 Bottles of 100 Tablets

NDC 42806-082-05 Bottles of 500 Tablets

Buspirone Hydrochloride Tablets USP, 7.5 mg are available as white to off-white, oval-shaped tablets, debossed “€” to the left and “83” to the right of score on one side and plain on the other side, and packaged in bottles of 100 and 500 tablets.

NDC 42806-083-01 Bottles of 100 Tablets

NDC 42806-083-05 Bottles of 500 Tablets

Buspirone Hydrochloride Tablets USP, 10 mg are available as white to off-white, round beveled-edge tablets, scored on one side and debossed “€” above “84” on the other side, and packaged in bottles of 100 and 500 tablets.

NDC 42806-084-01 Bottles of 100 Tablets

NDC 42806-084-05 Bottles of 500 Tablets

BusPIRone Hydrochloride Tablets USP, 12.5 mg are available as white to off-white, unscored tablets, debossed "€" above "135" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.

NDC 42806-085-01 Bottles of 100 Tablets

NDC 42806-085-05 Bottles of 500 Tablets

BusPIRone Hydrochloride Tablets USP, 15 mg are available as white to off-white, [scored](#) tablets that can either be bisected or trisected, debossed “5” on each trisect segment, and debossed “€” and “85” on bisect segments, and packaged in bottles of 100 and 500 tablets.

NDC 42806-085-01 Bottles of 100 Tablets

NDC 42806-085-05 Bottles of 500 Tablets

BusPIRone Hydrochloride Tablets USP, 30 mg are available as white to off-white, [scored](#) tablets that can either be bisected or trisected, debossed “10” on each trisect segment, and debossed “€” and “86” on bisect segments, and packaged in bottles of 60 and 500 tablets.

NDC 42806-086-60 Bottles of 60 Tablets

NDC 42806-085-05 Bottles of 500 Tablets

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

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.

REFERENCES

1. American Psychiatric Association, Ed.: Diagnostic and Statistical Manual of Mental Disorders—III, American Psychiatric Association, May 1980.

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Epic Pharma, LLC

Laurelton, NY 11413

Rev. 08-2023-00

MF082REV08/23

OE1546

Buspirone Hydrochloride Tablets, USP

Patient Instruction Sheet

Rx Only

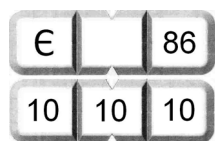
HOW TO USE:

Buspirone Hydrochloride Tablets USP, 15 mg and 30 mg

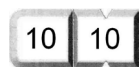
Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.

This tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages:

If your doctor prescribed the 30 mg tablet:



30 mg
(the entire tablet)



20 mg
(two-thirds of a tablet)



10 mg
(one-third of a tablet)



15 mg
(one-half of a tablet)

If your doctor prescribed the 15 mg tablet:



15 mg

(the entire tablet)



10 mg

(two-thirds of a tablet)



5 mg

(one-third of a tablet)

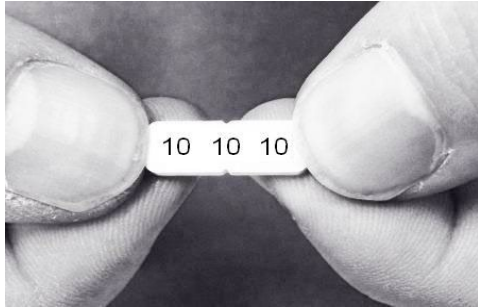


7.5 mg

(one-half of a tablet)

€85 on 15 mg and €86 on 30 mg tablet

To break a tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo. Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).



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BuSpar[®]

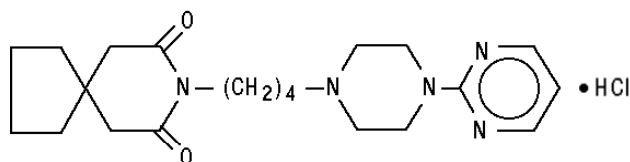
(buspirone HCl, USP)

(Patient Instruction Sheet Included)

DESCRIPTION

BuSpar[®] (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 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione monohydrochloride. The empirical formula $C_{21}H_{31}N_5O_2 \cdot HCl$ is represented by the following structural formula:



BuSpar is supplied as tablets for oral administration containing 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 and 30 mg tablets are provided in the DIVIDOSE[®] tablet design. These 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). BuSpar Tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 30 mg tablet also contains iron oxide.

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 D₂-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

BuSpar 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 BuSpar have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see **DOSAGE AND ADMINISTRATION**).

A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher blood levels of unchanged buspirone than would be predicted from results of single-dose studies.

An *in vitro* protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels

of free buspirone *in vivo*, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An *in vitro* study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.

Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by cytochrome P450 3A4 (CYP3A4). (See **PRECAUTIONS: Drug Interactions**.) Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to BuSpar (buspirone hydrochloride) do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/mL, less than 1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.

In a single-dose study using ¹⁴C-labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 mg to 40 mg is about 2 to 3 hours.

Special Populations

Age and Gender Effects

After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C_{max}) were observed between elderly and younger subjects or between men and women.

Hepatic Impairment

After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see **PRECAUTIONS**).

Renal Impairment

After multiple-dose administration of buspirone to renally impaired ($Cl_{cr} = 10\text{--}70\text{ mL/min/1.73 m}^2$) patients, steady-state AUC of buspirone increased 4-fold compared with healthy ($Cl_{cr} \geq 80\text{ mL/min/1.73 m}^2$) subjects (see **PRECAUTIONS**).

Race Effects

The effects of race on the pharmacokinetics of buspirone have not been studied.

INDICATIONS AND USAGE

BuSpar is indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of BuSpar 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 BuSpar 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, III¹ 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 BuSpar 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 BuSpar for 1 year without ill effect. Therefore, the physician who elects to use BuSpar for extended periods should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

BuSpar is 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 DRUG INTERACTIONS)

WARNINGS

The administration of BuSpar 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 BuSpar (buspirone hydrochloride) has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (in particular, MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for emergence of serotonin syndrome.

The concomitant use of buspirone with MAOIs intended to treat depression is contraindicated. Buspirone should also not be started in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. There have been no reports involving the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a reversible MAOI such as linezolid or intravenous methylene blue in a patient taking buspirone. Buspirone should be discontinued before initiating treatment with the reversible MAOI [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS].

If concomitant use of buspirone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of buspirone with serotonin precursors (such as tryptophan) is not recommended.

Treatment with buspirone and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS

General

Interference with Cognitive and Motor Performance

Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar (buspirone hydrochloride) with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients

Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying 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 (eg, 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 (ie, represent akathisia). See **ADVERSE REACTIONS: Postmarketing Experience**.

Information for Patients

To assure safe and effective use of BuSpar, 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 BuSpar.
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 BuSpar.
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 BuSpar (buspirone hydrochloride) consistently, either always with or always without food.
- 9 During your treatment with BuSpar, 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 WARNINGS, DOSAGE AND ADMINISTRATION AND CONCOMITANT DRUG)

Amitriptyline: After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{\max} , AUC, and C_{\min}) of amitriptyline or its metabolite nortriptyline were observed.

Diazepam: After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{\max} , AUC, and C_{\min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

Haloperidol: In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.

Nefazodone: (see **Inhibitors and Inducers of Cytochrome P450 3A4 [CYP3A4]**)

Trazodone: There is one report suggesting that the concomitant use of Desyrel[®] (trazodone hydrochloride) and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

Triazolam/Flurazepam: Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.

Other Psychotropics: Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.

Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4)

Buspirone has been shown *in vitro* to be metabolized by CYP3A4. This finding is consistent with the *in vivo* interactions observed between buspirone and the following:

Diltiazem and Verapamil: In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased AUC and C_{max} of buspirone 3.4-fold while diltiazem increased AUC and C_{max} 5.5-fold and 4-fold, respectively.) Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.

Erythromycin: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C_{max} and 6-fold increase in AUC). These

pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Grapefruit Juice: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C_{\max} ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.

Itraconazole: In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C_{\max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (eg, 2.5 mg q.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.

Nefazodone: In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{\max} and up to 50-fold in AUC) and statistically 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 (eg, 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.

Pregnancy: Teratogenic Effects

Pregnancy Category B: No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have *not* been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

The effect of BuSpar (buspirone hydrochloride) on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.

Nursing Mothers

The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. BuSpar administration to nursing women should be avoided if clinically possible.

Pediatric Use

The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6-week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses studied were 7.5 mg to 30 mg b.i.d. (15–60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.

Geriatric Use

In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.

There were no effects of age on the pharmacokinetics of buspirone (see **CLINICAL PHARMACOLOGY: Special Populations**).

Use in Patients With Impaired Hepatic or Renal Function

Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a lengthened half-life of buspirone. Therefore, the administration of BuSpar to patients with severe hepatic or renal impairment cannot be recommended (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS (See also PRECAUTIONS)

Commonly Observed

The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment

One guide to the relative clinical importance of adverse events associated with BuSpar 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 BuSpar 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 BuSpar (buspirone hydrochloride) patients who participated in 4-week, controlled trials comparing BuSpar 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	BuSpar (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	—
Neurological		
Numbness	2	—
Paresthesia	1	—
Incoordination	1	—
Tremor	1	—
Skin		
Skin Rash	1	—
Miscellaneous		
Headache	6	3
Fatigue	4	4
Weakness	2	—
Sweating/Clamminess	1	—

*Events reported by at least 1% of BuSpar patients are included.

—Incidence less than 1%.

Other Events Observed During the Entire Premarketing Evaluation of BuSpar

During its premarketing assessment, BuSpar was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000

subjects from this group who took multiple doses of BuSpar in the dose range for which BuSpar is being recommended (ie, the modal daily dose of BuSpar fell between 10 mg and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to BuSpar varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to BuSpar (buspirone hydrochloride) treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the **PRECAUTIONS** section.

The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.

Cardiovascular

Frequent was nonspecific chest pain; infrequent were syncope, hypotension, and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.

Central Nervous System

Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.

EENT

Frequent were tinnitus, sore throat, and nasal congestion; infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.

Endocrine

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 BuSpar treatment has not been determined.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

BuSpar (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 with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between BuSpar and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.

Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.

Although there is no direct evidence that BuSpar causes physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BuSpar misuse or abuse (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Signs and Symptoms

In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with BuSpar alone. Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD₅₀ values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 550 times the recommended human daily dose.

Recommended Overdose Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.

DOSAGE AND ADMINISTRATION

The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 mg to 30 mg per day were commonly employed.

The bioavailability of buspirone is increased when given with food as compared to the fasted state (see **CLINICAL PHARMACOLOGY**). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.

When buspirone is to be given with a potent inhibitor of CYP3A4, the dosage recommendations described in the **PRECAUTIONS: Drug Interactions** section should be followed.

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 BuSpar. Conversely, at least 14 days should be allowed after stopping BuSpar before starting an MAOI antidepressant (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Use of BuSpar with (Reversible) MAOIs, Such as Linezolid or Methylene Blue

Do not start BuSpar 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 DRUG INTERACTIONS).

In some cases, a patient already receiving therapy with BuSpar 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, BuSpar 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 BuSpar 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 BuSpar is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see CONTRAINDICATIONS, WARNINGS and DRUG INTERACTIONS).

HOW SUPPLIED

BuSpar[®] (buspirone hydrochloride tablets, USP) Tablets, 5 mg and 10 mg (white, ovoid-rectangular with score, MJ logo, strength and the name BuSpar embossed) are available in bottles of 100.

5 mg tablets

NDC 0087-0818-41 Bottles of 100

10 mg tablets

NDC 0087-0819-41 Bottles of 100

Tablets, 15 mg white, in the DIVIDOSE[®] tablet design imprinted with the MJ logo, are available in bottles of 60 and 180. Tablets, 30 mg pink, in the DIVIDOSE[®] tablet design imprinted with the MJ logo, are available in bottles of 60. The 15 mg and 30 mg tablets are scored so that they can be either bisected or trisected. The 15 mg tablet has ID number 822 on one side and on the reverse side, the number 5 on each trisect segment. The 30 mg tablet has ID number 824 on one side and on the reverse side, the number 10 on each trisect segment.

15 mg tablets

NDC 0087-0822-32 Bottles of 60

NDC 0087-0822-33 Bottles of 180

30 mg tablets

NDC 0087-0824-81 Bottles of 60

Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see USP controlled room temperature]. Dispense in a tight, light-resistant container (USP).

REFERENCE

1. American Psychiatric Association, Ed.: Diagnostic and Statistical Manual of Mental Disorders—III, American Psychiatric Association, May 1980.

Synthroid[®] is the registered trademark of Abbott Laboratories.

Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Rev XXX XXXX

BuSpar[®] (buspirone HCl, USP) Patient Instruction Sheet

Rx only

HOW TO USE:

BuSpar[®] (buspirone HCl, USP)

15 mg and 30 mg Tablets

in convenient DIVIDOSE[®] tablet form

Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.

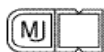
This DIVIDOSE tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages.

If your doctor
prescribed the
30 mg tablet:

30 mg
(the entire tablet)



20 mg
(two thirds of a tablet)



10 mg
(one third of a tablet)



15 mg
(one half of a tablet)



If your doctor
prescribed the
15 mg tablet:

15 mg
(the entire tablet)

10 mg
(two thirds of a tablet)

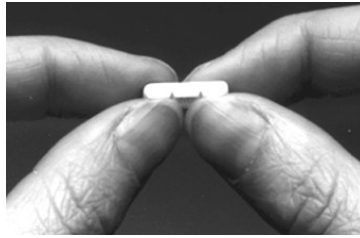
5 mg
(one third of a tablet)

7.5 mg
(one half of a tablet)

#822 on 15 mg and
824 on 30 mg tablet

To break a DIVIDOSE tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo.

Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).



Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Rev XXX XXXX

From: [raoffice](#)
To: [tina.lee](#); [Erik Korzik](#); [Ageel Fatmi](#)
Subject: Fwd: Buspirone Tablets Model Labeling
Date: Wednesday, December 7, 2016 11:53:32 AM
Attachments: [image003.png](#)
[Buspirone Tablets Model Labeling.pdf](#)

Get [Outlook for Android](#)

From: Pyon, Sunny <Sunny.Pyon@fda.hhs.gov>
Sent: Wednesday, December 7, 2016 10:46:50 AM
Cc: Pyon, Sunny
Subject: Buspirone Tablets Model Labeling

Dear Sir/Madam,

Your abbreviated new drug application (ANDA) relies on a reference listed drug (RLD) that has been withdrawn. The Office of Generic Drugs (OGD) has determined that the RLD labeling has become inaccurate and outdated; therefore, in accordance with the draft guidance for industry on *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016), the labeling updates have been attached.

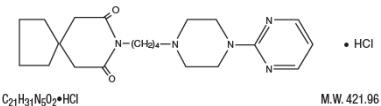
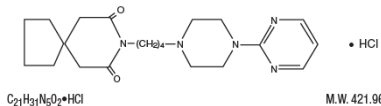
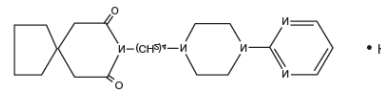
Thank you,

Sunny Pyon, Pharm.D.
Labeling Project Manager
Office of Generic Drugs, CDER
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993



• This email and any files transmitted with it are confidential and intended solely for the use of the individual or entity to whom they are addressed. If you are not the named addressee you should not disseminate, distribute or copy this e-mail. Please notify the sender immediately by e-mail if you have received this e-mail by mistake and delete this e-mail from your system. If you are not the intended recipient you are notified that disclosing, copying, distributing or taking any action in reliance on the contents of this information is strictly prohibited.

The proposed Epic prescribing information for tablets with new strengths is identical to the Reference Listed Drug's tablets prescribing information except the yellow highlights and is identical to Epic current FDA approved tablets prescribing information except the green highlights.

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
Buspirone Hydrochloride Tablets, USP Rx Only (Patient Instruction Sheet Included)	Buspirone Hydrochloride Tablets, USP Rx Only (Patient Instruction Sheet Included)	BuSpar[®] (buspirone HCl, USP) (Patient Instruction Sheet Included)
DESCRIPTION Buspirone hydrochloride tablets are an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.	DESCRIPTION Buspirone hydrochloride tablets, USP are an antianxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs.	DESCRIPTION BuSpar [®] (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 421.96. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4,5]decane-7,9-dione monohydrochloride. The empirical formula C ₂₁ H ₃₁ N ₅ O ₂ •HCl is represented by the following structural formula:	Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 421.96. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4,5]decane-7,9-dione monohydrochloride. The empirical formula C ₂₁ H ₃₁ N ₅ O ₂ •HCl is represented by the following structural formula:	Buspirone hydrochloride is a white crystalline, water soluble compound with a molecular weight of 422.0. Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4,5]decane-7,9-dione monohydrochloride. The empirical formula C ₂₁ H ₃₁ N ₅ O ₂ •HCl is represented by the following structural formula:
 <p>Chemical structure of Buspirone hydrochloride (Epic Proposed). The structure shows a spirocyclic system consisting of a 4,5-decane-7,9-dione ring fused to a 4,5-decane-7,9-dione ring, with a piperazine ring attached to the 8-position of the decane-7,9-dione ring. The empirical formula is C₂₁H₃₁N₅O₂•HCl and the molecular weight is 421.96.</p>	 <p>Chemical structure of Buspirone hydrochloride (Epic Current Approved). The structure shows a spirocyclic system consisting of a 4,5-decane-7,9-dione ring fused to a 4,5-decane-7,9-dione ring, with a piperazine ring attached to the 8-position of the decane-7,9-dione ring. The empirical formula is C₂₁H₃₁N₅O₂•HCl and the molecular weight is 421.96.</p>	 <p>Chemical structure of Buspirone hydrochloride (Reference Listed Drug). The structure shows a spirocyclic system consisting of a 4,5-decane-7,9-dione ring fused to a 4,5-decane-7,9-dione ring, with a piperazine ring attached to the 8-position of the decane-7,9-dione ring. The empirical formula is C₂₁H₃₁N₅O₂•HCl and the molecular weight is 422.0.</p>
Each tablet, for oral administration, contains 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg or 30 mg of buspirone hydrochloride, USP (equivalent to 2.3 mg, 3.4 mg, 4.6 mg, 6.9 mg, 9.1 mg, 11.4 mg, 13.7 mg and 27.4 mg of buspirone free base, respectively). The 2.5 mg, 3.75 mg 12.5	Each tablet, for oral administration, contains 5 mg, 7.5 mg, 10 mg, 15 mg or 30 mg of buspirone hydrochloride, USP (equivalent to 4.6 mg, 6.9 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	BuSpar is supplied as tablets for oral administration containing 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

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<p>mg tablets are unscored. 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 and 30 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: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.</p>	<p>tablet can also provide a 2.5 mg dose, and the 10 mg tablet can provide a 5 mg dose. The 15 mg and 30 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: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.</p>	<p>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 and 30 mg tablets are provided in the DIVIDOSE® tablet design. These 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). BuSpar Tablets contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 30 mg tablet also contains iron oxide.</p>
<p>CLINICAL PHARMACOLOGY</p> <p>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.</p>	<p>CLINICAL PHARMACOLOGY</p> <p>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.</p>	<p>CLINICAL PHARMACOLOGY</p> <p>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.</p>
<p>Buspirone has moderate affinity for brain D₂-dopamine receptors. Some studies do suggest that</p>	<p>Buspirone has moderate affinity for brain D₂-dopamine receptors. Some studies do suggest that</p>	<p>Buspirone has moderate affinity for brain D₂-dopamine receptors. Some studies do suggest that</p>

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buspirone may have indirect effects on other neurotransmitter systems.	buspirone may have indirect effects on other neurotransmitter systems.	buspirone may have indirect effects on other neurotransmitter systems.
<p>Buspirone hydrochloride 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.</p>	<p>Buspirone hydrochloride 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.</p>	<p>BuSpar 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.</p>
<p>The effects of food upon the bioavailability of buspirone hydrochloride tablets have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see DOSAGE AND ADMINISTRATION).</p>	<p>The effects of food upon the bioavailability of buspirone hydrochloride tablets have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see DOSAGE AND ADMINISTRATION).</p>	<p>The effects of food upon the bioavailability of BuSpar have been studied in eight subjects. They were given a 20 mg dose with and without food; the area under the plasma concentration-time curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116%, respectively, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone (see DOSAGE AND ADMINISTRATION).</p>
<p>A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher</p>	<p>A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher</p>	<p>A multiple-dose study conducted in 15 subjects suggests that buspirone has nonlinear pharmacokinetics. Thus, dose increases and repeated dosing may lead to somewhat higher</p>

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blood levels of unchanged buspirone than would be predicted from results of single-dose studies.	blood levels of unchanged buspirone than would be predicted from results of single-dose studies.	blood levels of unchanged buspirone than would be predicted from results of single-dose studies.
<p>An in vitro protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone in vivo, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An in vitro study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.</p>	<p>An in vitro protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone in vivo, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An in vitro study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.</p>	<p>An in vitro protein binding study indicated that approximately 86% of buspirone is bound to plasma proteins. It was also observed that aspirin increased the plasma levels of free buspirone by 23%, while flurazepam decreased the plasma levels of free buspirone by 20%. However, it is not known whether these drugs cause similar effects on plasma levels of free buspirone in vivo, or whether such changes, if they do occur, cause clinically significant differences in treatment outcome. An in vitro study indicated that buspirone did not displace highly protein-bound drugs such as phenytoin, warfarin, and propranolol from plasma protein, and that buspirone may displace digoxin.</p>
<p>Buspirone is metabolized primarily by oxidation, which in vitro has been shown to be mediated by cytochrome P450 3A4 (CYP3A4) (see PRECAUTIONS, Drug Interactions). Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to buspirone hydrochloride do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/mL, less than</p>	<p>Buspirone is metabolized primarily by oxidation, which in vitro has been shown to be mediated by cytochrome P450 3A4 (CYP3A4) (see PRECAUTIONS, Drug Interactions). Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to buspirone hydrochloride do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/mL, less than</p>	<p>Buspirone is metabolized primarily by oxidation, which in vitro has been shown to be mediated by cytochrome P450 3A4 (CYP3A4) (see PRECAUTIONS, Drug Interactions). Several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP), are produced. In animal models predictive of anxiolytic potential, 1-PP has about one quarter of the activity of buspirone, but is present in up to 20-fold greater amounts. However, this is probably not important in humans: blood samples from humans chronically exposed to BuSpar (buspirone hydrochloride) do not exhibit high levels of 1-PP; mean values are approximately 3 ng/mL and the highest human blood level recorded among 108 chronically dosed patients was 17 ng/mL, less than</p>

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1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.	1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.	1/200th of 1-PP levels found in animals given large doses of buspirone without signs of toxicity.
In a single-dose study using ¹⁴ C-labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is about 2 to 3 hours.	In a single-dose study using ¹⁴ C-labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is about 2 to 3 hours.	In a single-dose study using ¹⁴ C-labeled buspirone, 29% to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites; fecal excretion accounted for 18% to 38% of the dose. The average elimination half-life of unchanged buspirone after single doses of 10 to 40 mg is about 2 to 3 hours.
Special Populations Age and Gender Effects After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C _{max}) were observed between elderly and younger subjects or between men and women.	Special Populations Age and Gender Effects After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C _{max}) were observed between elderly and younger subjects or between men and women.	Special Populations Age and Gender Effects After single or multiple doses in adults, no significant differences in buspirone pharmacokinetics (AUC and C _{max}) were observed between elderly and younger subjects or between men and women.
Hepatic Impairment After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see PRECAUTIONS).	Hepatic Impairment After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see PRECAUTIONS).	Hepatic Impairment After multiple-dose administration of buspirone to patients with hepatic impairment, steady-state AUC of buspirone increased 13-fold compared with healthy subjects (see PRECAUTIONS).
Renal Impairment After multiple-dose administration of buspirone to renally impaired (Cl _{cr} =10-70 mL/min/1.73 m ²) patients, steady state AUC of buspirone increased 4-fold compared with healthy (Cl _{cr} ≥80 mL/min/1.73 m ²) subjects (see PRECAUTIONS).	Renal Impairment After multiple-dose administration of buspirone to renally impaired (Cl _{cr} =10-70 mL/min/1.73 m ²) patients, steady state AUC of buspirone increased 4-fold compared with healthy (Cl _{cr} ≥80 mL/min/1.73 m ²) subjects (see PRECAUTIONS).	Renal Impairment After multiple-dose administration of buspirone to renally impaired (Cl _{cr} =10-70 mL/min/1.73 m ²) patients, steady state AUC of buspirone increased 4-fold compared with healthy (Cl _{cr} ≥80 mL/min/1.73 m ²) subjects (see PRECAUTIONS).
Race Effects	Race Effects	Race Effects

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The effects of race on the pharmacokinetics of buspirone have not been studied.	The effects of race on the pharmacokinetics of buspirone have not been studied.	The effects of race on the pharmacokinetics of buspirone have not been studied.
<p>INDICATIONS AND USAGE</p> <p>Buspirone hydrochloride tablets are indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.</p>	<p>INDICATIONS AND USAGE</p> <p>Buspirone hydrochloride tablets are indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.</p>	<p>INDICATIONS AND USAGE</p> <p>BuSpar is indicated for the management of anxiety disorders or the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.</p>
<p>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, III¹ as follows:</p>	<p>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, III¹ as follows:</p>	<p>The efficacy of BuSpar 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 BuSpar 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, III¹ as follows:</p>
<p>Generalized, persistent anxiety (of at least 1 month continual duration), manifested by symptoms from three of the four following categories:</p> <ol style="list-style-type: none"> Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle. 	<p>Generalized, persistent anxiety (of at least 1 month continual duration), manifested by symptoms from three of the four following categories:</p> <ol style="list-style-type: none"> Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle. 	<p>Generalized, persistent anxiety (of at least 1 month continual duration), manifested by symptoms from three of the four following categories:</p> <ol style="list-style-type: none"> Motor tension: shakiness, jitteriness, jumpiness, trembling, tension, muscle aches, fatigability, inability to relax, eyelid twitch, furrowed brow, strained face, fidgeting, restlessness, easy startle.

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<p>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.</p> <p>3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.</p> <p>4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling “on edge,” irritability, impatience.</p>	<p>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.</p> <p>3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.</p> <p>4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling “on edge,” irritability, impatience.</p>	<p>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.</p> <p>3. Apprehensive expectation: anxiety, worry, fear, rumination, and anticipation of misfortune to self or others.</p> <p>4. Vigilance and scanning: hyperattentiveness resulting in distractibility, difficulty in concentrating, insomnia, feeling “on edge,” irritability, impatience.</p>
<p>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.</p>	<p>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.</p>	<p>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.</p>
<p>The effectiveness of buspirone hydrochloride c 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.</p>	<p>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.</p>	<p>The effectiveness of BuSpar 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 BuSpar for 1 year without ill effect. Therefore, the physician who elects to use BuSpar for extended periods should periodically reassess the usefulness of the drug for the individual patient.</p>

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<p>CONTRAINDICATIONS</p> <p>Buspirone hydrochloride tablets are contraindicated in patients hypersensitive to buspirone hydrochloride.</p>	<p>CONTRAINDICATIONS</p> <p>Buspirone hydrochloride tablets are contraindicated in patients hypersensitive to buspirone hydrochloride.</p>	<p>CONTRAINDICATIONS</p> <p>BuSpar is contraindicated in patients hypersensitive to buspirone hydrochloride.</p>
<p>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.</p>	<p>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.</p>	<p>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.</p>
<p>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 DRUG INTERACTIONS)</p>	<p>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 DRUG INTERACTIONS)</p>	<p>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 DRUG INTERACTIONS)</p>
<p>WARNINGS</p> <p>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.</p>	<p>WARNINGS</p> <p>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.</p>	<p>WARNINGS</p> <p>The administration of BuSpar 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 BuSpar (buspirone hydrochloride) has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.</p>
<p>Serotonin Syndrome</p>	<p>Serotonin Syndrome</p>	<p>Serotonin Syndrome</p>

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The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (in particular, MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.	The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (in particular, MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.	The development of a potentially life-threatening serotonin syndrome has been reported with SNRIs SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (in particular, MAOIs, including reversible MAOIs such as linezolid and intravenous methylene blue), or with antipsychotics or other dopamine antagonists.
Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for emergence of serotonin syndrome.	Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for emergence of serotonin syndrome.	Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular changes (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for emergence of serotonin syndrome.
The concomitant use of buspirone with MAOIs intended to treat depression is contraindicated. Buspirone should also not be started in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. There have been no reports involving the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a reversible MAOI such as	The concomitant use of buspirone with MAOIs intended to treat depression is contraindicated. Buspirone should also not be started in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. There have been no reports involving the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a reversible MAOI such as	The concomitant use of buspirone with MAOIs intended to treat depression is contraindicated. Buspirone should also not be started in a patient who is being treated with reversible MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. There have been no reports involving the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a reversible MAOI such as

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linezolid or intravenous methylene blue in a patient taking buspirone. Buspirone should be discontinued before initiating treatment with the reversible MAOI [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS].	linezolid or intravenous methylene blue in a patient taking buspirone. Buspirone should be discontinued before initiating treatment with the reversible MAOI [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS].	linezolid or intravenous methylene blue in a patient taking buspirone. Buspirone should be discontinued before initiating treatment with the reversible MAOI [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION AND DRUG INTERACTIONS].
If concomitant use of buspirone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.	If concomitant use of buspirone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.	If concomitant use of buspirone with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
The concomitant use of buspirone with serotonin precursors (such as tryptophan) is not recommended.	The concomitant use of buspirone with serotonin precursors (such as tryptophan) is not recommended.	The concomitant use of buspirone with serotonin precursors (such as tryptophan) is not recommended.
Treatment with buspirone and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.	Treatment with buspirone and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.	Treatment with buspirone and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.
Because buspirone hydrochloride tablets have no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.	Because buspirone hydrochloride tablets have no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.	Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.
<p>PRECAUTIONS</p> <p>General</p> <p>Interference with Cognitive and Motor Performance</p> <p>Studies indicate that buspirone is less sedating than other anxiolytics and that it does not produce</p>	<p>PRECAUTIONS</p> <p>General</p> <p>Interference with Cognitive and Motor Performance</p> <p>Studies indicate that buspirone is less sedating than other anxiolytics and that it does not produce</p>	<p>PRECAUTIONS</p> <p>General</p> <p>Interference with Cognitive and Motor Performance</p> <p>Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce</p>

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significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.	significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.	significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.
While formal studies of the interaction of buspirone hydrochloride with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.	While formal studies of the interaction of buspirone hydrochloride with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.	While formal studies of the interaction of BuSpar (buspirone hydrochloride) with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.
Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients Because buspirone does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone hydrochloride tablets, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.	Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients Because buspirone does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone hydrochloride tablets, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.	Potential for Withdrawal Reactions in Sedative/Hypnotic/Anxiolytic Drug-Dependent Patients Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS-depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying 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	The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle	The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle

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cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.	cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.	cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.
<p>Possible Concerns Related to Buspirone’s Binding to Dopamine Receptors</p> <p>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 (eg. 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.</p>	<p>Possible Concerns Related to Buspirone’s Binding to Dopamine Receptors</p> <p>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 (eg. 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.</p>	<p>Possible Concerns Related to Buspirone’s Binding to Dopamine Receptors</p> <p>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 (eg. 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.</p>
<p>Information for Patients</p> <p>To assure safe and effective use of buspirone hydrochloride tablets, the following information and instructions should be given to patients:</p> <ol style="list-style-type: none"> 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. Do not take an MAOI within 2 weeks of stopping buspirone unless directed to do so by your physician. 	<p>Information for Patients</p> <p>To assure safe and effective use of buspirone hydrochloride tablets, the following information and instructions should be given to patients:</p> <ol style="list-style-type: none"> 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. Do not take an MAOI within 2 weeks of stopping buspirone unless directed to do so by your physician. 	<p>Information for Patients</p> <p>To assure safe and effective use of BuSpar, the following information and instructions should be given to patients:</p> <ol style="list-style-type: none"> 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. Do not take an MAOI within 2 weeks of stopping buspirone unless directed to do so by your physician.

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<p>3. Do not start buspirone if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.</p> <p>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.</p> <p>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.</p> <p>6. Inform your physician if you are breast-feeding an infant.</p> <p>7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.</p> <p>8. You should take buspirone hydrochloride tablets consistently, either always with or always without food.</p> <p>9. During your treatment with buspirone hydrochloride tablets, avoid drinking large amounts of grapefruit juice.</p>	<p>3. Do not start buspirone if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.</p> <p>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.</p> <p>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.</p> <p>6. Inform your physician if you are breast-feeding an infant.</p> <p>7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.</p> <p>8. You should take buspirone hydrochloride tablets consistently, either always with or always without food.</p> <p>9. During your treatment with buspirone hydrochloride tablets, avoid drinking large amounts of grapefruit juice.</p>	<p>3. Do not start buspirone if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.</p> <p>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 BuSpar.</p> <p>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 BuSpar.</p> <p>6. Inform your physician if you are breast-feeding an infant.</p> <p>7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.</p> <p>8. You should take BuSpar (buspirone hydrochloride) consistently, either always with or always without food.</p> <p>9. During your treatment with BuSpar, avoid drinking large amounts of grapefruit juice.</p>
<p>Laboratory Tests</p> <p>There are no specific laboratory tests recommended.</p>	<p>Laboratory Tests</p> <p>There are no specific laboratory tests recommended.</p>	<p>Laboratory Tests</p> <p>There are no specific laboratory tests recommended.</p>
<p>Drug Interactions</p> <p>Psychotropic Agents</p>	<p>Drug Interactions</p> <p>Psychotropic Agents</p>	<p>Drug Interactions</p> <p>Psychotropic Agents</p>

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<i>MAO inhibitors:</i> 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.	<i>MAO inhibitors:</i> 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.	<i>MAO inhibitors:</i> 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 CONCOMITANT DRUG)	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 CONCOMITANT DRUG)	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 CONCOMITANT DRUG)
<i>Amitriptyline:</i> After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) of amitriptyline or its metabolite nortriptyline were observed.	<i>Amitriptyline:</i> After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) of amitriptyline or its metabolite nortriptyline were observed.	<i>Amitriptyline:</i> After addition of buspirone to the amitriptyline dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) of amitriptyline or its metabolite nortriptyline were observed.
<i>Diazepam:</i> After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.	<i>Diazepam:</i> After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.	<i>Diazepam:</i> After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max} , AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.
<i>Haloperidol:</i> In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum	<i>Haloperidol:</i> In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum	<i>Haloperidol:</i> In a study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum

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haloperidol concentrations. The clinical significance of this finding is not clear.	haloperidol concentrations. The clinical significance of this finding is not clear.	haloperidol concentrations. The clinical significance of this finding is not clear.
<i>Nefazodone:</i> (see Inhibitors and Inducers of Cytochrome P450 3A4 [CYP3A4])	<i>Nefazodone:</i> (see Inhibitors and Inducers of Cytochrome P450 3A4 [CYP3A4])	<i>Nefazodone:</i> (see Inhibitors and Inducers of Cytochrome P450 3A4 [CYP3A4])
<i>Trazodone:</i> There is one report suggesting that the concomitant use of Desyrel® (trazodone hydrochloride) and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.	<i>Trazodone:</i> There is one report suggesting that the concomitant use of Desyrel® (trazodone hydrochloride) and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.	<i>Trazodone:</i> There is one report suggesting that the concomitant use of Desyrel® (trazodone hydrochloride) and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.
<i>Triazolam/Flurazepam:</i> Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.	<i>Triazolam/Flurazepam:</i> Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.	<i>Triazolam/Flurazepam:</i> Coadministration of buspirone with either triazolam or flurazepam did not appear to prolong or intensify the sedative effects of either benzodiazepine.
<i>Other Psychotropics:</i> Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.	<i>Other Psychotropics:</i> Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.	<i>Other Psychotropics:</i> Because the effects of concomitant administration of buspirone with most other psychotropic drugs have not been studied, the concomitant use of buspirone with other CNS-active drugs should be approached with caution.
Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) Buspirone has been shown in vitro to be metabolized by CYP3A4. This finding is consistent with the in vivo interactions observed between buspirone and the following:	Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) Buspirone has been shown in vitro to be metabolized by CYP3A4. This finding is consistent with the in vivo interactions observed between buspirone and the following:	Inhibitors and Inducers of Cytochrome P450 3A4 (CYP3A4) Buspirone has been shown in vitro to be metabolized by CYP3A4. This finding is consistent with the in vivo interactions observed between buspirone and the following:
<i>Diltiazem and Verapamil:</i> In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased	<i>Diltiazem and Verapamil:</i> In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased	<i>Diltiazem and Verapamil:</i> In a study of nine healthy volunteers, coadministration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) or diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations (verapamil increased

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AUC and C _{max} of buspirone 3.4-fold while diltiazem increased AUC and C _{max} 5.5-fold and 4-fold, respectively). Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.	AUC and C _{max} of buspirone 3.4-fold while diltiazem increased AUC and C _{max} 5.5-fold and 4-fold, respectively). Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.	AUC and C _{max} of buspirone 3.4-fold while diltiazem increased AUC and C _{max} 5.5-fold and 4-fold, respectively). Adverse events attributable to buspirone may be more likely during concomitant administration with either diltiazem or verapamil. Subsequent dose adjustment may be necessary and should be based on clinical assessment.
<i>Erythromycin:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C _{max} and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.	<i>Erythromycin:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C _{max} and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.	<i>Erythromycin:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with erythromycin (1.5 g/day for 4 days) increased plasma buspirone concentrations (5-fold increase in C _{max} and 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side effects attributable to buspirone. If the two drugs are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustment of either drug should be based on clinical assessment.
<i>Grapefruit juice:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C _{max} ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.	<i>Grapefruit juice:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C _{max} ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.	<i>Grapefruit juice:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with grapefruit juice (200 mL double-strength t.i.d. for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C _{max} ; 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid drinking such large amounts of grapefruit juice.
<i>Itraconazole:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C _{max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side	<i>Itraconazole:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C _{max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side	<i>Itraconazole:</i> In a study in healthy volunteers, coadministration of buspirone (10 mg as a single dose) with itraconazole (200 mg/day for 4 days) increased plasma buspirone concentrations (13-fold increase in C _{max} and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of side

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effects attributable to buspirone. 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.	effects attributable to buspirone. 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.	effects attributable to buspirone. 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.
<i>Nefazodone:</i> In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C _{max} and up to 50-fold in AUC) and statistically 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.	<i>Nefazodone:</i> In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C _{max} and up to 50-fold in AUC) and statistically 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.	<i>Nefazodone:</i> In a study of steady-state pharmacokinetics in healthy volunteers, coadministration of buspirone (2.5 or 5 mg b.i.d.) with nefazodone (250 mg b.i.d.) resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C _{max} and up to 50-fold in AUC) and statistically 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.
<i>Rifampin:</i> 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	<i>Rifampin:</i> 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	<i>Rifampin:</i> 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

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buspirone may need adjusting to maintain anxiolytic effect.	buspirone may need adjusting to maintain anxiolytic effect.	buspirone may need adjusting to maintain anxiolytic effect.
<i>Other Inhibitors and Inducers of CYP3A4:</i> 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.	<i>Other Inhibitors and Inducers of CYP3A4:</i> 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.	<i>Other Inhibitors and Inducers of CYP3A4:</i> 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 <i>Cimetidine:</i> 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.	Other Drugs <i>Cimetidine:</i> 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.	Other Drugs <i>Cimetidine:</i> 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,	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,	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,

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digoxin, and Synthroid®. In vitro, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.	digoxin, and Synthroid®. In vitro, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.	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).	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).	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.	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.	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.	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.	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 <i>Salmonella typhimurium</i> (Ames Test) or mouse lymphoma L5178YTK+ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or	With or without metabolic activation, buspirone did not induce point mutations in five strains of <i>Salmonella typhimurium</i> (Ames Test) or mouse lymphoma L5178YTK+ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or	With or without metabolic activation, buspirone did not induce point mutations in five strains of <i>Salmonella typhimurium</i> (Ames Test) or mouse lymphoma L5178YTK+ cell cultures, nor was DNA damage observed with buspirone in Wi-38 human cells. Chromosomal aberrations or

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abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.	abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.	abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.
Pregnancy: Teratogenic Effects <i>Pregnancy Category B</i> <p>No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have not been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.</p>	Pregnancy: Teratogenic Effects <i>Pregnancy Category B</i> <p>No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have not been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.</p>	Pregnancy: Teratogenic Effects <i>Pregnancy Category B</i> <p>No fertility impairment or fetal damage was observed in reproduction studies performed in rats and rabbits at buspirone doses of approximately 30 times the maximum recommended human dose. In humans, however, adequate and well-controlled studies during pregnancy have not been performed. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.</p>
Labor and Delivery <p>The effect of buspirone hydrochloride on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.</p>	Labor and Delivery <p>The effect of buspirone hydrochloride on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.</p>	Labor and Delivery <p>The effect of BuSpar (buspirone hydrochloride) on labor and delivery in women is unknown. No adverse effects were noted in reproduction studies in rats.</p>
Nursing Mothers <p>The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. Buspirone hydrochloride administration to nursing women should be avoided if clinically possible.</p>	Nursing Mothers <p>The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. Buspirone hydrochloride administration to nursing women should be avoided if clinically possible.</p>	Nursing Mothers <p>The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. BuSpar administration to nursing women should be avoided if clinically possible.</p>
Pediatric Use <p>The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6- week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses</p>	Pediatric Use <p>The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6- week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses</p>	Pediatric Use <p>The safety and effectiveness of buspirone were evaluated in two placebo-controlled 6- week trials involving a total of 559 pediatric patients (ranging from 6 to 17 years of age) with GAD. Doses</p>

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<p>studied were 7.5 mg to 30 mg b.i.d. (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.</p>	<p>studied were 7.5 mg to 30 mg b.i.d. (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.</p>	<p>studied were 7.5 mg to 30 mg b.i.d. (15-60 mg/day). There were no significant differences between buspirone and placebo with regard to the symptoms of GAD following doses recommended for the treatment of GAD in adults. Pharmacokinetic studies have shown that, for identical doses, plasma exposure to buspirone and its active metabolite, 1-PP, are equal to or higher in pediatric patients than adults. No unexpected safety findings were associated with buspirone in these trials. There are no long-term safety or efficacy data in this population.</p>
<p>Geriatric Use</p> <p>In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.</p>	<p>Geriatric Use</p> <p>In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.</p>	<p>Geriatric Use</p> <p>In one study of 6632 patients who received buspirone for the treatment of anxiety, 605 patients were ≥ 65 years old and 41 were ≥ 75 years old; the safety and efficacy profiles for these 605 elderly patients (mean age = 70.8 years) were similar to those in the younger population (mean age = 43.3 years). Review of spontaneously reported adverse clinical events has not identified differences between elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out.</p>
<p>There were no effects of age on the pharmacokinetics of buspirone (see CLINICAL PHARMACOLOGY, Special Populations).</p>	<p>There were no effects of age on the pharmacokinetics of buspirone (see CLINICAL PHARMACOLOGY, Special Populations).</p>	<p>There were no effects of age on the pharmacokinetics of buspirone (see CLINICAL PHARMACOLOGY, Special Populations).</p>
<p>Use in Patients With Impaired Hepatic or Renal Function</p> <p>Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a</p>	<p>Use in Patients With Impaired Hepatic or Renal Function</p> <p>Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a</p>	<p>Use in Patients With Impaired Hepatic or Renal Function</p> <p>Buspirone is metabolized by the liver and excreted by the kidneys. A pharmacokinetic study in patients with impaired hepatic or renal function demonstrated increased plasma levels and a</p>

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lengthened half-life of buspirone. Therefore, the administration of buspirone hydrochloride tablets to patients with severe hepatic or renal impairment cannot be recommended (see CLINICAL PHARMACOLOGY).	lengthened half-life of buspirone. Therefore, the administration of buspirone hydrochloride tablets to patients with severe hepatic or renal impairment cannot be recommended (see CLINICAL PHARMACOLOGY).	lengthened half-life of buspirone. Therefore, the administration of BuSpar to patients with severe hepatic or renal impairment cannot be recommended (see CLINICAL PHARMACOLOGY).
<p>ADVERSE REACTIONS (See also PRECAUTIONS.)</p> <p>Commonly Observed</p> <p>The more commonly observed untoward events associated with the use of buspirone hydrochloride tablets not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.</p>	<p>ADVERSE REACTIONS (See also PRECAUTIONS.)</p> <p>Commonly Observed</p> <p>The more commonly observed untoward events associated with the use of buspirone hydrochloride tablets not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.</p>	<p>ADVERSE REACTIONS (See also PRECAUTIONS.)</p> <p>Commonly Observed</p> <p>The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.</p>
<p>Associated with Discontinuation of Treatment</p> <p>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</p>	<p>Associated with Discontinuation of Treatment</p> <p>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</p>	<p>Associated with Discontinuation of Treatment</p> <p>One guide to the relative clinical importance of adverse events associated with BuSpar 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 BuSpar 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</p>

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<p>Incidence in Controlled Clinical Trials</p> <p>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 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.</p>	<p>Incidence in Controlled Clinical Trials</p> <p>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 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.</p>	<p>Incidence in Controlled Clinical Trials</p> <p>The table that follows enumerates adverse events that occurred at a frequency of 1% or more among BuSpar (buspirone hydrochloride) patients who participated in 4-week, controlled trials comparing BuSpar 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.</p>																																	
<p>TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE</p> <p>IN PLACEBO-CONTROLLED CLINICAL TRIALS*</p> <p>(Percent of Patients Reporting)</p> <table border="1"> <tr> <th>Adverse Experience</th><th>Buspirone Hydrochloride (n=477)</th><th>Placebo (n=464)</th></tr> <tr> <td>Cardiovascular</td><td></td><td></td></tr> <tr> <td>Tachycardia/Palpitations</td><td>1</td><td>1</td></tr> <tr> <td>CNS</td><td></td><td></td></tr> </table>	Adverse Experience	Buspirone Hydrochloride (n=477)	Placebo (n=464)	Cardiovascular			Tachycardia/Palpitations	1	1	CNS			<p>TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE</p> <p>IN PLACEBO-CONTROLLED CLINICAL TRIALS*</p> <p>(Percent of Patients Reporting)</p> <table border="1"> <tr> <th>Adverse Experience</th><th>Buspirone Hydrochloride tablet (n=477)</th><th>Placebo (n=464)</th></tr> <tr> <td>Cardiovascular</td><td></td><td></td></tr> <tr> <td>Tachycardia/Palpitations</td><td>1</td><td>1</td></tr> </table>	Adverse Experience	Buspirone Hydrochloride tablet (n=477)	Placebo (n=464)	Cardiovascular			Tachycardia/Palpitations	1	1	<p>TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE</p> <p>IN PLACEBO-CONTROLLED CLINICAL TRIALS*</p> <p>(Percent of Patients Reporting)</p> <table border="1"> <tr> <th>Adverse Experience</th><th>BuSpar (n=477)</th><th>Placebo (n=464)</th></tr> <tr> <td>Cardiovascular</td><td></td><td></td></tr> <tr> <td>Tachycardia/Palpitations</td><td>1</td><td>1</td></tr> <tr> <td>CNS</td><td></td><td></td></tr> </table>	Adverse Experience	BuSpar (n=477)	Placebo (n=464)	Cardiovascular			Tachycardia/Palpitations	1	1	CNS		
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Dizziness	12	3	CNS			Dizziness	12	3
Drowsiness	10	9	Dizziness	12	3	Drowsiness	10	9
Nervousness	5	1	Drowsiness	10	9	Nervousness	5	1
Insomnia	3	3	Nervousness	5	1	Insomnia	3	3
Lightheadedness	3	-	Insomnia	3	3	Lightheadedness	3	-
Decreased Concentration	2	2	Lightheadedness	3	-	Decreased Concentration	2	2
Excitement	2	-	Decreased Concentration	2	2	Excitement	2	-
Anger/Hostility	2	-	Excitement	2	-	Anger/Hostility	2	-
Confusion	2	-	Anger/Hostility	2	-	Confusion	2	-
Depression	2	2	Confusion	2	-	Depression	2	2
EENT			Depression	2	2	EENT		
Blurred Vision	2	-	EENT			Blurred Vision	2	-
Gastrointestinal			Blurred Vision	2	-	Gastrointestinal		
Nausea	8	5	Gastrointestinal			Nausea	8	5
Dry Mouth	3	4	Nausea	8	5	Dry Mouth	3	4
Abdominal/Gastric Distress	2	2	Dry Mouth	3	4	Abdominal/Gastric Distress	2	2
Diarrhea	2	-	Abdominal/Gastric Distress	2	2	Diarrhea	2	-
Constipation	1	2	Diarrhea	2	-	Constipation	1	2
Vomiting	1	2	Constipation	1	2	Vomiting	1	2
Musculoskeletal			Vomiting	1	2	Musculoskeletal		
Musculoskeletal Aches/Pains	1	-	Musculoskeletal			Musculoskeletal Aches/Pains	1	-
Neurological			Musculoskeletal Aches/Pains	1	-	Neurological		
Numbness	2	-	Neurological			Numbness	2	-
Paresthesia	1	-	Numbness	2	-	Paresthesia	1	-
Incoordination	1	-	Paresthesia	1	-	Incoordination	1	-
Tremor	1	-	Incoordination	1	-	Tremor	1	-
Skin			Tremor	1	-	Skin		
Skin Rash	1	-	Skin			Skin Rash	1	-
Miscellaneous			Skin Rash	1	-	Miscellaneous		

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<p>Other Events Observed During the Entire Premarketing Evaluation of Buspirone Hydrochloride Tablets</p> <p>During its premarketing assessment, buspirone hydrochloride was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of buspirone hydrochloride in the dose range for which buspirone is being recommended (i.e., the modal daily dose of buspirone hydrochloride fell between 10 mg and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone hydrochloride varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to buspirone hydrochloride treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.</p>	<p>Other Events Observed During the Entire Premarketing Evaluation of Buspirone Hydrochloride Tablets</p> <p>During its premarketing assessment, buspirone hydrochloride was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of buspirone hydrochloride in the dose range for which buspirone is being recommended (i.e., the modal daily dose of buspirone hydrochloride fell between 10 mg and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone hydrochloride varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to buspirone hydrochloride treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.</p>	<p>Other Events Observed During the Entire Premarketing Evaluation of BuSpar</p> <p>During its premarketing assessment, BuSpar was evaluated in over 3500 subjects. This section reports event frequencies for adverse events occurring in approximately 3000 subjects from this group who took multiple doses of BuSpar in the dose range for which BuSpar is being recommended (i.e., the modal daily dose of BuSpar fell between 10 mg and 30 mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to BuSpar varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies, a causal relationship to BuSpar (buspirone hydrochloride) treatment cannot be determined. The list includes all undesirable events reasonably associated with the use of the drug.</p>																																							

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The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the PRECAUTIONS section.	The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the PRECAUTIONS section.	The following enumeration by organ system describes events in terms of their relative frequency of reporting in this data base. Events of major clinical importance are also described in the PRECAUTIONS section.
The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.	The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.	The following definitions of frequency are used: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare events are those occurring in less than 1/1000 patients.
Cardiovascular Frequent was nonspecific chest pain; infrequent were syncope, hypotension, and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.	Cardiovascular Frequent was nonspecific chest pain; infrequent were syncope, hypotension, and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.	Cardiovascular Frequent was nonspecific chest pain; infrequent were syncope, hypotension, and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, and bradycardia.
Central Nervous System Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.	Central Nervous System Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.	Central Nervous System Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, involuntary movements, slowed reaction time, suicidal ideation, and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis.
EENT Frequent were tinnitus, sore throat, and nasal congestion; infrequent were redness and itching of the eyes, altered taste, altered smell, and	EENT Frequent were tinnitus, sore throat, and nasal congestion; infrequent were redness and itching of the eyes, altered taste, altered smell, and	EENT Frequent were tinnitus, sore throat, and nasal congestion; infrequent were redness and itching of the eyes, altered taste, altered smell, and

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conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.	conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.	conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes.
Endocrine Rare were galactorrhea and thyroid abnormality.	Endocrine Rare were galactorrhea and thyroid abnormality.	Endocrine 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.	Gastrointestinal Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon, and rectal bleeding; rare was burning of the tongue.	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.	Genitourinary Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis, and nocturia.	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.	Musculoskeletal Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias; rare was muscle weakness.	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.	Respiratory Infrequent were hyperventilation, shortness of breath, and chest congestion; rare was epistaxis.	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.	Sexual Function Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence.	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.	Skin Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, and blisters; rare were acne and thinning of nails.	Skin Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, and blisters; rare were acne and thinning of nails.

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Clinical Laboratory Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia, and thrombocytopenia.	Clinical Laboratory Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia, and thrombocytopenia.	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.	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.	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 capsules treatment has not been determined.	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.	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 BuSpar 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.	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.	Do not have ADVERSE REACTIONS contact in the labeling of RLD tablets.
DRUG ABUSE AND DEPENDENCE	DRUG ABUSE AND DEPENDENCE	DRUG ABUSE AND DEPENDENCE

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<p>Controlled Substance Class</p> <p>Buspirone hydrochloride is not a controlled substance.</p>	<p>Controlled Substance Class</p> <p>Buspirone hydrochloride is not a controlled substance.</p>	<p>Controlled Substance Class</p> <p>BuSpar (buspirone hydrochloride) is not a controlled substance.</p>
<p>Physical and Psychological Dependence</p> <p>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 with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between buspirone hydrochloride tablets and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.</p>	<p>Physical and Psychological Dependence</p> <p>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 with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between buspirone hydrochloride tablets and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.</p>	<p>Physical and Psychological Dependence</p> <p>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 with a history of recreational drug or alcohol usage were studied in two double-blind clinical investigations. None of the subjects were able to distinguish between BuSpar and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Studies in monkeys, mice, and rats have indicated that buspirone lacks potential for abuse.</p>
<p>Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.</p>	<p>Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.</p>	<p>Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependency.</p>
<p>Although there is no direct evidence that buspirone hydrochloride tablets cause physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone hydrochloride tablets misuse or abuse (e.g.,</p>	<p>Although there is no direct evidence that buspirone hydrochloride tablets cause physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone hydrochloride tablets misuse or abuse (e.g.,</p>	<p>Although there is no direct evidence that BuSpar causes physical dependence or drug-seeking behavior, it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of BuSpar misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).</p>

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
development of tolerance, incrementation of dose, drug-seeking behavior).	development of tolerance, incrementation of dose, drug-seeking behavior).	
<p>OVERDOSAGE</p> <p>Signs and Symptoms</p> <p>In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with buspirone hydrochloride tablets alone. Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD₅₀ values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 550 times the recommended human daily dose.</p>	<p>OVERDOSAGE</p> <p>Signs and Symptoms</p> <p>In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with buspirone hydrochloride tablets alone. Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD₅₀ values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 550 times the recommended human daily dose.</p>	<p>OVERDOSAGE</p> <p>Signs and Symptoms</p> <p>In clinical pharmacology trials, doses as high as 375 mg/day were administered to healthy male volunteers. As this dose was approached, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. A few cases of overdosage have been reported, with complete recovery as the usual outcome. No deaths have been reported following overdosage with BuSpar alone. Rare cases of intentional overdosage with a fatal outcome were invariably associated with ingestion of multiple drugs and/or alcohol, and a causal relationship to buspirone could not be determined. Toxicology studies of buspirone yielded the following LD₅₀ values: mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg. These dosages are 160 to 550 times the recommended human daily dose.</p>
<p>Recommended Overdose Treatment</p> <p>General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.</p>	<p>Recommended Overdose Treatment</p> <p>General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.</p>	<p>Recommended Overdose Treatment</p> <p>General symptomatic and supportive measures should be used along with immediate gastric lavage. Respiration, pulse, and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known to buspirone, and dialyzability of buspirone has not been determined.</p>
DOSAGE AND ADMINISTRATION	DOSAGE AND ADMINISTRATION	DOSAGE AND ADMINISTRATION

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 to 30 mg per day were commonly employed.	The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 to 30 mg per day were commonly employed.	The recommended initial dose is 15 mg daily (7.5 mg b.i.d.). To achieve an optimal therapeutic response, at intervals of 2 to 3 days the dosage may be increased 5 mg per day, as needed. The maximum daily dosage should not exceed 60 mg per day. In clinical trials allowing dose titration, divided doses of 20 to 30 mg per day were commonly employed.
The bioavailability of buspirone is increased when given with food as compared to the fasted state (see CLINICAL PHARMACOLOGY). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.	The bioavailability of buspirone is increased when given with food as compared to the fasted state (see CLINICAL PHARMACOLOGY). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.	The bioavailability of buspirone is increased when given with food as compared to the fasted state (see CLINICAL PHARMACOLOGY). Consequently, patients should take buspirone in a consistent manner with regard to the timing of dosing; either always with or always without food.
When buspirone is to be given with a potent inhibitor of CYP3A4, the dosage recommendations described in the PRECAUTIONS, Drug Interactions section should be followed.	When buspirone is to be given with a potent inhibitor of CYP3A4, the dosage recommendations described in the PRECAUTIONS, Drug Interactions section should be followed.	When buspirone is to be given with a potent inhibitor of CYP3A4, the dosage recommendations described in the PRECAUTIONS, Drug Interactions section should be followed.
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 buspirone hydrochloride tablets . Conversely, at least 14 days should be allowed after stopping buspirone hydrochloride tablets before starting an MAOI antidepressant (see CONTRAINDICATIONS and DRUG INTERACTIONS).	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 buspirone hydrochloride tablets . Conversely, at least 14 days should be allowed after stopping buspirone hydrochloride tablets before starting an MAOI antidepressant (see CONTRAINDICATIONS and DRUG INTERACTIONS).	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 BuSpar . Conversely, at least 14 days should be allowed after stopping BuSpar before starting an MAOI antidepressant (see CONTRAINDICATIONS and DRUG INTERACTIONS).
Use of Buspirone with (Reversible) MAOIs, Such as Linezolid or Methylene Blue	Use of Buspirone with (Reversible) MAOIs, Such as Linezolid or Methylene Blue	Use of BuSpar with (Reversible) MAOIs, Such as Linezolid or Methylene Blue



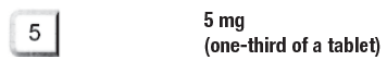
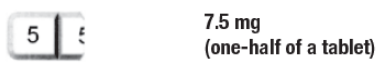


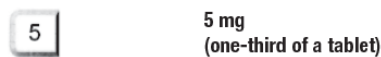
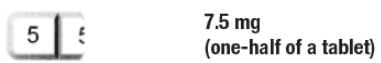
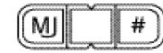

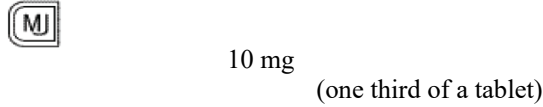
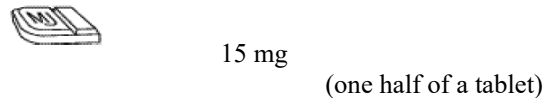
Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
<p>Do not start buspirone hydrochloride tablets in a patient who is being 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 DRUG INTERACTIONS).</p>	<p>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 DRUG INTERACTIONS).</p>	<p>Do not start BuSpar 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 DRUG INTERACTIONS).</p>
<p>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).</p>	<p>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).</p>	<p>In some cases, a patient already receiving therapy with BuSpar 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, BuSpar 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 BuSpar may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).</p>













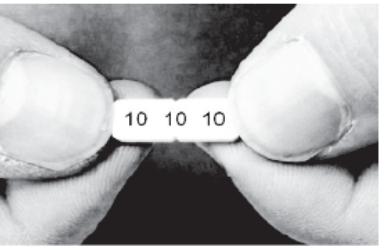
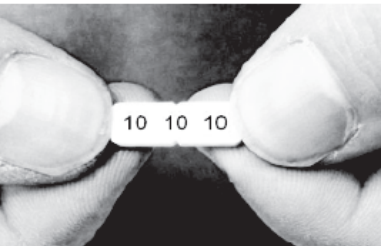

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
<p>The risk of administering methylene blue by non-intravenous routes (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 DRUG INTERACTIONS).</p>	<p>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 DRUG INTERACTIONS).</p>	<p>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 BuSpar is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see CONTRAINDICATIONS, WARNINGS and DRUG INTERACTIONS).</p>
HOW SUPPLIED	HOW SUPPLIED	HOW SUPPLIED
<p>Buspirone Hydrochloride Tablets USP, 2.5 mg are available as white to off-white, round, unscored tablets, debossed "C" above "78" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-078-01 Bottles of 100 Tablets</p> <p>NDC 42806-078-05 Bottles of 500 Tablets</p>	N/A	N/A
<p>Buspirone Hydrochloride Tablets USP, 3.75 mg are available as white to off-white, round, unscored tablets, debossed "C" above "79" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-079-01 Bottles of 100 Tablets</p> <p>NDC 42806-079-05 Bottles of 500 Tablets</p>	N/A	N/A

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
<p>Buspirone Hydrochloride Tablets USP, 5 mg are available as white to off-white, round, beveled-edge tablets, scored on one side and debossed "C" above "82" on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-082-01 Bottles of 100 Tablets</p> <p>NDC 42806-082-05 Bottles of 500 Tablets</p>	<p>Buspirone Hydrochloride Tablets USP, 5 mg are available as white to off-white, round, beveled-edge tablets, scored on one side and debossed "C" above "82" on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-082-01 Bottles of 100 Tablets</p> <p>NDC 42806-082-05 Bottles of 500 Tablets</p>	<p>BuSpar® (buspirone hydrochloride tablets, USP) Tablets, 5 mg and 10 mg (white, ovoid-rectangular with score, MJ logo, strength and the name BuSpar embossed) are available in bottles of 100.</p> <p>5 mg tablets</p> <p>NDC 0087-0818-41 Bottles of 100</p>
<p>Buspirone Hydrochloride Tablets USP, 7.5 mg are available as white to off-white, oval-shaped tablets, debossed "C" to the left and "83" to the right of score on one side and plain on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-083-01 Bottles of 100 Tablets</p> <p>NDC 42806-083-05 Bottles of 500 Tablets</p>	<p>Buspirone Hydrochloride Tablets USP, 7.5 mg are available as white to off-white, oval-shaped tablets, debossed "C" to the left and "83" to the right of score on one side and plain on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-083-01 Bottles of 100 Tablets</p> <p>NDC 42806-083-05 Bottles of 500 Tablets</p>	<p>RLD labeling does not include 7.5 mg tablet's description.</p>
<p>Buspirone Hydrochloride Tablets USP, 10 mg are available as white to off-white, round beveled-edge tablets, scored on one side and debossed "C" above "84" on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-084-01 Bottles of 100 Tablets</p> <p>NDC 42806-084-05 Bottles of 500 Tablets</p>	<p>Buspirone Hydrochloride Tablets USP, 10 mg are available as white to off-white, round beveled-edge tablets, scored on one side and debossed "C" above "84" on the other side, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-084-01 Bottles of 100 Tablets</p> <p>NDC 42806-084-05 Bottles of 500 Tablets</p>	<p>10 mg tablets</p> <p>NDC 0087-0819-41 Bottles of 100</p>

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
<p>Buspirone Hydrochloride Tablets USP, 12.5 mg are available as white to off-white, unscored tablets, debossed "C" above "135" on upper punch and plain on the lower punch, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-135-01 Bottles of 100 Tablets</p> <p>NDC 42806-135-05 Bottles of 500 Tablets</p>	N/A	N/A
<p>Buspirone Hydrochloride Tablets USP, 15 mg are available as white to off-white, scored tablets that can either be bisected or trisected, debossed "5" on each trisect segment, and debossed "C" and "85" on bisect segments, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-085-01 Bottles of 100 Tablets</p> <p>NDC 42806-085-05 Bottles of 500 Tablets</p>	<p>Buspirone Hydrochloride Tablets USP, 15 mg are available as white to off-white, scored tablets that can either be bisected or trisected, debossed "5" on each trisect segment, and debossed "C" and "85" on bisect segments, and packaged in bottles of 100 and 500 tablets.</p> <p>NDC 42806-085-01 Bottles of 100 Tablets</p> <p>NDC 42806-085-05 Bottles of 500 Tablets</p>	<p>Tablets, 15 mg white, in the DIVIDOSE® tablet design imprinted with the MJ logo, are available in bottles of 60 and 180. Tablets, 30 mg pink, in the DIVIDOSE® tablet design imprinted with the MJ logo, are available in bottles of 60. The 15 mg and 30 mg tablets are scored so that they can be either bisected or trisected. The 15 mg tablet has ID number 822 on one side and on the reverse side, the number 5 on each trisect segment. The 30 mg tablet has ID number 824 on one side and on the reverse side, the number 10 on each trisect segment.</p> <p>15 mg tablets</p> <p>NDC 0087-0822-32 Bottles of 60 NDC 0087-0822-33 Bottles of 180</p>
<p>Buspirone Hydrochloride Tablets USP, 30 mg are available as white to off-white, scored tablets that can either be bisected or trisected, debossed "10" on each trisect segment, and debossed "C" and "86" on bisect segments, and packaged in bottles of 60 and 500 tablets.</p> <p>NDC 42806-086-60</p>	<p>Buspirone Hydrochloride Tablets USP, 30 mg are available as white to off-white, scored tablets that can either be bisected or trisected, debossed "10" on each trisect segment, and debossed "C" and "86" on bisect segments, and packaged in bottles of 60 and 500 tablets.</p> <p>NDC 42806-086-60</p>	<p>30 mg tablets</p> <p>NDC 0087-0824-81 Bottles of 60</p>

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
<p>Bottles of 60 Tablets</p> <p>NDC 42806-086-05</p> <p>Bottles of 500 Tablets</p>	<p>Bottles of 60 Tablets</p> <p>NDC 42806-086-05</p> <p>Bottles of 500 Tablets</p>	
<p>Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].</p> <p>Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).</p> <p>KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.</p>	<p>Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].</p> <p>Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).</p> <p>KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.</p>	<p>Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see USP controlled room temperature].</p> <p>Dispense in a tight, light-resistant container (USP).</p>
<p>REFERENCES</p> <p>1. American Psychiatric Association, Ed.: Diagnostic and Statistical Manual of Mental Disorders—III, American Psychiatric Association, May 1980.</p>	<p>REFERENCES</p> <p>1. American Psychiatric Association, Ed.: Diagnostic and Statistical Manual of Mental Disorders—III, American Psychiatric Association, May 1980.</p>	<p>REFERENCES</p> <p>1. American Psychiatric Association, Ed.: Diagnostic and Statistical Manual of Mental Disorders—III, American Psychiatric Association, May 1980.</p>
<p>All Product/Brand names are the trademarks of their respective owners.</p>	<p>All Product/Brand names are the trademarks of their respective owners.</p>	<p>Synthroid® is the registered trademark of Abbott Laboratories.</p>
<p>Distributed by:</p> <p>Epic Pharma, LLC</p> <p>Laurelton, NY 11413</p> <p>Rev. 08-2023-00</p> <p>MF082REV08/23</p> <p>OE1546</p>	<p>Distributed by:</p> <p>Epic Pharma, LLC</p> <p>Laurelton, NY 11413</p> <p>Rev. 02-2017-00</p> <p>MF082REV02/17</p> <p>OE1546</p>	<p>Bristol-Myers Squibb Company</p> <p>Princeton, NJ 08543 USA</p> <p>Rev November 2010</p>
<p>Bupirone Hydrochloride Tablets, USP</p> <p>Patient Instruction Sheet</p> <p>Rx Only</p>	<p>Bupirone Hydrochloride Tablets, USP</p> <p>Patient Instruction Sheet</p> <p>Rx Only</p>	<p>BuSpar®</p> <p>(bupirone HCl, USP)</p> <p>Patient Instruction Sheet</p>

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
		Rx Only
HOW TO USE: Buspirone Hydrochloride Tablets USP, 15 mg and 30 mg	HOW TO USE: Buspirone Hydrochloride Tablets USP, 15 mg and 30 mg	HOW TO USE: BuSpar® (buspirone HCl, USP) 15 mg and 30 mg Tablets In convenient DIVIDOSE® tablet form
Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.	Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.	Response to buspirone varies among individuals. Your physician may find it necessary to adjust your dosage to obtain the proper response.
This tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages:	This tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages:	This DIVIDOSE tablet design makes dosage adjustments easy. Each tablet is scored and can be broken accurately to provide any of the following dosages:
<p>If your doctor prescribed the 30 mg tablet:</p> <div data-bbox="205 857 583 1230">  <p>15 mg (the entire tablet)</p>  <p>10 mg (two-thirds of a tablet)</p>  <p>5 mg (one-third of a tablet)</p>  <p>7.5 mg (one-half of a tablet)</p> </div>	<p>If your doctor prescribed the 30 mg tablet:</p> <div data-bbox="777 857 1155 1230">  <p>15 mg (the entire tablet)</p>  <p>10 mg (two-thirds of a tablet)</p>  <p>5 mg (one-third of a tablet)</p>  <p>7.5 mg (one-half of a tablet)</p> </div>	<p>If your doctor prescribed the 30 mg tablet:</p> <div data-bbox="1354 857 1894 1289">  <p>30 mg (the entire tablet)</p>  <p>20 mg (two third of a tablet)</p>  <p>10 mg (one third of a tablet)</p>  <p>15 mg (one half of a tablet)</p> </div>
If your doctor prescribed the 15 mg tablet:	If your doctor prescribed the 15 mg tablet:	If your doctor prescribed the 15 mg tablet:

Epic Proposed Tablet Labeling Adding Strengths: 2.5m 3.75 and 12.5 mg – 2023.08	Epic Current Approved Tablet Labeling– 2017.02	Reference Listed Drug, BuSpar Tablets, Prescribing Information – Provided by FDA via email on 12/07/2016
 15 mg (the entire tablet)  10 mg (two-thirds of a tablet)  5 mg (one-third of a tablet)  7.5 mg (one-half of a tablet)	 15 mg (the entire tablet)  10 mg (two-thirds of a tablet)  5 mg (one-third of a tablet)  7.5 mg (one-half of a tablet)	 15 mg (the entire tablet)  10 mg (two third of a tablet)  5 mg (one third of a tablet)  7.5 mg (one half of a tablet)
€85 on 15 mg and €86 on 30 mg	€85 on 15 mg and €86 on 30 mg	#822 on 15 mg and #824 on 30 mg tablet
To break a scored tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo. Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).	To break a scored tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo. Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).	To break a DIVIDOSE tablet accurately and easily, hold the tablet between your thumbs and index fingers close to the appropriate tablet score (groove) as shown in the photo. Then, with the tablet score facing you, apply pressure and snap the tablet segments apart (segments breaking incorrectly should not be used).
		
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Laurelton, NY 11413 Rev. 08-2023-00 OE1546	Laurelton, NY 11413 Rev. 02-2017-00 OE1546	Rev November 2010