PRODUCT MONOGRAPH

Pr *CO* BUSPIRONE

Buspirone Hydrochloride Tablets

5 mg & 10 mg

USP

Anxiolytic

Cobalt Pharmaceuticals Inc.
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Mississauga, Ontario
L5N 2B8

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CO BUSPIRONE

Buspirone Hydrochloride Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet/ 5 mg , 10 mg	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CO Buspirone (buspirone hydrochloride) is indicated for short term symptomatic relief of excessive anxiety in patients with Generalized Anxiety Disorder (GAD).

The effectiveness of buspirone in long-term use (i.e., more than 4 weeks) has not been evaluated in controlled clinical trials.

Eight three-way short-term, controlled clinical trials involving buspirone, diazepam and placebo are considered central to the evaluation of buspirone as an anxiolytic agent. In four of the eight clinical trials, buspirone demonstrated a significant difference from placebo. In the other four trials, there was no significant difference between buspirone and placebo, but a significantly greater improvement was observed with diazepam than with placebo. The adverse effect profiles of buspirone and diazepam in these clinical trials were, however, different.

Geriatrics (> 65 years of age):
Buspirone has not been systematically evaluated in the elderly patient population.

Pediatrics:
The safety and effectiveness of buspirone in individuals under the age of 18 years have not been established.

CONTRAINDICATIONS

- *CO* Buspirone is contraindicated in patients with hypersensitivity to buspirone hydrochloride or any other ingredient in the formulation. For a complete listing see Dosage Forms, Composition and Packaging section of the product monograph.

- *CO* Buspirone is contraindicated in patients with severe hepatic or severe renal impairment.

WARNINGS AND PRECAUTIONS

General

MAO Inhibitors
The occurrence of elevated blood pressure in patients receiving both buspirone and a monoamine oxidase inhibitor (MAOI) has been reported. Therefore, it is recommended that buspirone should not be used concomitantly with a MAOI.

Extrapyramidal Symptoms
Since buspirone may bind to central dopaminergic receptors, the possibility of acute and chronic changes in dopamine-mediated neurological function (e.g., dystonia, pseudo-parkinsonism, akathisia and tardive dyskinesia) should be considered.

Use of Buspirone in patients previously treated with a benzodiazepine
Patients who have previously taken benzodiazepines may be less likely to respond to buspirone than those who have not. In two clinical studies to date, substitution of buspirone did not ameliorate or prevent withdrawal symptoms in either abrupt or gradual withdrawal from various benzodiazepines following long-term use. Therefore, if it is considered desirable to switch a patient who has been receiving benzodiazepine therapy to buspirone, the benzodiazepine should first be withdrawn gradually. A drug-free interval is desirable between withdrawal of the benzodiazepine and initiation of buspirone, in order to increase the likelihood of distinguishing between benzodiazepine withdrawal effects and unrelieved anxiety due to possible failure of buspirone in this category of patients. In patients requiring continued therapy and where a benzodiazepine washout period is not feasible, gradual benzodiazepine taper/withdrawal may be overlapped by buspirone therapy over a few weeks. Buspirone should not, however, be used to detoxify patients addicted to benzodiazepines.

Benzodiazepine rebound or withdrawal symptoms may occur over varying time periods depending in part on the type of drug and its effective elimination half-life. These symptoms may appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever and, occasionally seizures, and should be treated symptomatically.

Effects on Cognitive and Motor Performance:
In controlled studies in healthy volunteers, single doses of buspirone up to 20 mg had little effect on most tests of cognitive and psychomotor function, although performance on a vigilance task was impaired in a dose-related manner. The effect of higher single doses of buspirone on psychomotor performance has not been investigated.

Ten (10 mg) milligram of buspirone given three times daily for seven days to healthy volunteers produced considerable subjective sedation but no significant effect on psychomotor performance (no vigilance tasks were used in this study). It also caused transient dizziness, especially on standing and walking.

Until further experience is obtained with buspirone, patients should be warned not to operate an automobile or undertake activities requiring mental alertness, judgement and physical coordination, until they are reasonably certain that buspirone does not affect them adversely.

Carcinogenesis and Mutagenesis
No data is available.

Cardiovascular
No data is available.

Dependence/Tolerance
Preliminary animal and human investigations suggest that buspirone may be significantly devoid of potential for producing physical or psychological dependence, only extensive clinical experience with the drug will provide conclusive evidence. Meanwhile, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse and abuse.

Ear/Nose/Throat
No data is available.

Endocrine and Metabolism
No data is available.

Gastrointestinal
No data is available.

Genitourinary
No data is available.

Hematologic
No data is available.

Hepatic/Biliary/Pancreatic
Since it is metabolized by the liver, buspirone should be used with caution in the patients with a history of hepatic impairment. It is contraindicated in patients with severe hepatic impairment.

Immune
No data is available.

Neuroendocrine
Single doses of 30 mg or higher or buspirone resulted in significantly elevated plasma prolactin and growth hormone concentrations in normal volunteers. No effect was seen at lower doses. In another study, no such increases were observed after buspirone was administered in divided doses (10 mg t.i.d.) for 28 days.

Neurologic
Buspirone is not recommended for patients with a history of seizure disorders.

Long-Term Toxicity
Buspirone can bind to central serotonin and dopamine receptors. A question has been raised about is 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). Obviously, the question cannot be totally resolved at this point in time. Because its mechanism of action is not fully elucidated, long-term toxicity in the CNS or other organ systems cannot be predicted.

Ophthalmologic
No data is available.

Peri-Operative Considerations
No data is available.

Psychiatric
No data is available.

Renal
Since it is excreted by kidneys, buspirone should be used with caution in patients with a history of renal impairment. It is contraindicated in patients with severe renal impairment.

Respiratory
No data is available.

Sensitivity/Resistance
No data is available.

Sexual Function/Reproduction
No data is available.

Skin

No data is available.

Special Populations

Pregnant and Nursing Women: The safety of buspirone during pregnancy and lactation has not been established and, therefore, it should not be used in women of childbearing potential or nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus. Buspirone and its metabolites are excreted in milk in rats. The extent of excretion in human milk has not yet been determined. The effect of Buspirone on labor and delivery is unknown.

Pediatrics (< *18* years of age): The safety and effectiveness of buspirone in individuals under the age of 18 years have not been established.

Geriatrics (> 65 years of age): Buspirone has not been systematically evaluated in older patients. Although it would appear from limited pharmacokinetic and clinical studies that buspirone does not behave differently in the elderly, there is little known about the effects of buspirone in this age group at doses above 30 mg/day. Therefore, it is recommended that buspirone should be used in the elderly at doses not exceeding 30 mg/day for a duration not exceeding 4 weeks.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Commonly Observed

Side effects of Buspirone, if they occur, are generally observed at the beginning of drug therapy and usually subside with use of the medication and/or decreased dosage.

When patients receiving Buspirone were compared with patients receiving placebo, dizziness, headache, nervousness, lightheadedness, nausea, excitement, and sweating/clamminess were the only side effects occurring with significantly greater frequency ($p<0.10$) in the buspirone group than in the placebo group.

Associated with discontinuation of treatment

During controlled clinical efficacy trials, approximately 10% of 2200 anxious patients discontinued treatment due to an adverse event. The more common events associated with discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness and light-headed feeling; gastrointestinal disturbances (1.2%), primarily nausea; and miscellaneous disturbances (1.1%), primarily headache and fatigue.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Incidence in clinical trials

Adverse reactions reported in approximately 3000 subjects who participated in premarketing trials are listed below by body system. Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in less than 1/100 but at least 1/1000 patients, while rare events are those occurring in less than 1/1000 patients. In the absence of appropriate controls in some of the studies, a causal relationship to Buspirone can not be determined.

Allergic or Toxic:
Frequent: Skin rash, sore throat.

Autonomic:
Frequent: Dry mouth, sweating/clamminess, blurred vision, constipation.

Cardiovascular:
Frequent: Tachycardia/palpipations, chest pain.

Central Nervous System:
Frequent: Dizziness, headache, drowsiness, lightheadedness, insomnia, fatigue, nervousness, decreased concentration/abnormal thinking, excitement, depression, confusion, nightmares/vivid dreams, anger/hostility.

Gastrointestinal:
Frequent: Nausea, gastrointestinal distress, diarrhea, vomiting.

Miscellaneous:
Frequent: Tinnitus, muscle aches/pains, headache.

Neurologic:
Frequent: Paresthesia, weakness, incoordination, tremor, numbness.

Respiratory:
Frequent: Nasal congestion.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Allergic or Toxic:
Infrequent: Edema/facial edema, pruritus, chills/fever.
Rare: Photophobia, erythema, flu-like symptoms.

Autonomic:
Infrequent: Urinary frequency, retention and burning, flushing.

Cardiovascular:
Infrequent: Syncope, hypotension, hypertension.
Rare: Congestive heart failure, cerebrovascular accident, myocardial infarction, cardiomyopathy, bradycardia and EKG change.

Central Nervous System:
Infrequent: Depersonalization, noise intolerance, euphoria/feeling high, dissociative reaction, fear, loss of interest, dysphoria, hallucinations, seizures, suicidal thoughts.
Rare: Slurred speech, claustrophobia, cold intolerance, stupor, psychosis.

Endocrine:
Infrequent: Decreased and increased libido, weight gain, weight loss, menstrual irregularity/breakthrough bleeding.
Rare: Delayed ejaculation, impotence, galactorrhea, amenorrhea, thyroid abnormality.

Gastrointestinal:
Infrequent: Flatulence, increased appetite, anorexia, hypersalivation, rectal bleeding, irritable colon.
Rare: Burning tongue.

Miscellaneous:
Infrequent: Redness/itching of eyes, altered taste/smell, roaring sensation in head, malaise, easy bruising, dry skin, arthralgia, blisters, hair loss.
Rare: Acne, thinning of nails, sore eyes, inner ear abnormality, pressure on eyes, nocturia, enuresis, hiccups, voice loss, alcohol abuse.

Neurologic:
Infrequent: Muscle cramps and spasms, rigid/stiff muscles, involuntary movements, akathisia, slowed reaction time.
Rare: Tingling of limbs, stiff neck, rigidity of jaw.

Respiratory:
Infrequent: Shortness of breath, chest congestion, hyperventilation.
Rare: Epistaxis.

Abnormal Hematologic and Clinical Chemistry Findings

Clinical Laboratory
Infrequent: Increases in liver enzymes.
Rare: Eosinophilia, leukopenia, thrombocytopenia.

Post-Market Adverse Drug Reactions

Although treatment conditions and duration vary greatly, and a causal relationship of adverse events to buspirone cannot always be determined, spontaneous adverse event reports have included rare occurrences (less than 1/10,000) of the following adverse events:

Body as a whole: allergic reactions including urticaria, ecchymosis, angioedema.

CNS/Neurological: extrapyramidal symptoms, including dyskinesias (acute and delayed), dystonic reactions and cogwheel rigidity; depersonalization; emotional lability; hallucinations; psychosis, ataxias, and seizures; transient difficulty with recall; serotonin syndrome.

Miscellaneous: syncope; tunnel vision; urinary retention; and female galactorrhea.

DRUG INTERACTIONS

Drug-Drug Interactions

Amitriptyline
In a study in normal volunteers, no interaction of buspirone with amitriptyline was seen.

Diazepam
After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (Cmax, AUC, and Cmin) 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 another 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.

Monoamine Oxidase Inhibitors
Concomitant use of monoamine oxidase inhibitors and buspirone has been reported to cause an increase in blood pressure. Therefore, concomitant use of these medications is not recommended (see WARNINGS AND PRECAUTIONS).

Protein Binding
Buspirone does not displace from serum proteins drugs like phenytoin, propranolol, and warfarin that are highly protein-bound. However, there have been rare reports of prolonged prothrombin time when buspirone was added to the regimen of a patient treated with warfarin. *In vitro*, buspirone may displace less firmly protein-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 limited effect on the extent of binding of buspirone to plasma proteins.

SSRIs
Overall, there have been no major safety problems reported with the combination of buspirone and selective serotonin reuptake inhibitor antidepressants. Seizures have been reported rarely in patients taking this combination.

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

The concomitant use of buspirone with other CNS active drugs should be approached with caution (see WARNINGS AND PRECAUTIONS).

Potential Interaction with Drugs That Inhibit Cytochrome P450 3A4 (CYP3A4)

Buspirone has been shown *in vitro* to be metabolized by CYP3A4. This is consistent with the interaction observed between buspirone and erythromycin, itraconazole, or nefazodone, drugs that inhibit this isozyme. Consequently, when administered with a potent inhibitor of CYP3A4, a low dose of buspirone is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Diltiazem
In a study of nine healthy volunteers, administration of buspirone (10 mg as a single dose) with diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations. The AUC and Cmax of buspirone were increased 5.3-fold and 4-fold, respectively. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with diltiazem. Subsequent dose adjustments of either drug should be based on clinical response.

Erythromycin
The coadministration of buspirone (10 mg as a single dose) and erythromycin (1.5 g/day for 4 days) to healthy volunteers increased plasma buspirone concentrations (5-fold increase in Cmax and a 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an

increased incidence of adverse events attributable to buspirone. If buspirone and erythromycin are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Itraconazole

The coadministration of buspirone (10 mg as a single dose) and itraconazole (200 mg/day for 4 days) to healthy volunteers increased plasma buspirone concentrations (13-fold increase in Cmax and 19-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of adverse events attributable to buspirone. If buspirone and itraconazole are to be used in combination, a low dose of buspirone (e.g., 2.5 mg q.d.) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Nefazodone

The coadministration of buspirone (2.5 or 5 mg b.i.d.) And nefazodone (250 mg b.i.d.) to healthy volunteers resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in Cmax and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of buspirone metabolite, 1-pyrimidinylpiperazine. 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 mCPP (9%). Slight increase in Cmax were observed for nefazodone (8%) and its metabolite HO-NEF (11%).

The side effect profile for subjects receiving buspirone 2.5 mg b.i.d. and nefazodone 250 mg b.i.d. was similar to that for subjects receiving either drug alone. Subjects receiving buspirone 5 mg b.i.d. and nefazodone 250 mg b.i.d. experienced side effects such as lightheadedness, asthenia, dizziness, and somnolence. It is recommended that the dose of buspirone be lowered when administered with nefazodone. Subsequent dose adjustments of either drug should be based on clinical response.

Rifampicin

In a study in healthy volunteers, coadministration of buspirone (30 mg as a single dose) with rifampicin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in Cmax and 89.6% decrease in AUC) and pharmacodynamic effects of buspirone.

Verapamil

In a study of nine healthy volunteers, administration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) increased plasma buspirone concentrations. The AUC and Cmax of buspirone were increased 3.4-fold. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with verapamil. Subsequent dose adjustments of either drug should be based on clinical response.

Other Inhibitors and Inducers of CYP3A4

Substances that inhibit CYP3A4, such as ketoconazole of 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. 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, an adjustment of the dosage of buspirone may be necessary to maintain buspirone's anxiolytic effect.

Cimetidine
Coadministration of buspirone and cimetidine was found to increase Cmax (40%) and Tmax (2-fold) of buspirone, but had minimal effect on AUC of buspirone.

Drug-Food Interactions
Food may decrease the extent of presystemic clearance of buspirone.

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

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
There have been no reports to date of interference of buspirone with commonly employed clinical laboratory tests.

Drug-Lifestyle Interactions

Alcohol
In laboratory studies in healthy volunteers, buspirone in doses up to 20 mg did not potentiate the psychomotor impairment produced by relatively modest doses of alcohol. However, decreased contentedness or dysphoria was observed with a combination of alcohol and a 20 mg single dose of buspirone. Since no data are available on concomitant use of higher doses of buspirone and alcohol, it is prudent to advise patients to avoid alcohol during buspirone therapy.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CO Buspirone dosage should be individually adjusted, according to tolerance and response.

Elderly Patients:

Limited pharmacokinetic and clinical data have shown no difference in the effects of buspirone between elderly patients and healthy adult volunteers. However, until more information has accumulated in the elderly, it is recommended that the maximum daily dose should not exceed 30 mg for a duration not exceeding 4 weeks.

Note: If buspirone is administered to patients with compromised hepatic or renal function, careful monitoring will be required together with appropriate dosage adjustment.

Recommended Dose and Dosage Adjustment
The recommended initial dose is 5 mg two to three times daily. This may be titrated according to the needs of the patient and the daily dose increased by 5 mg increments every two to three days up to a maximum of 45 mg daily in divided doses. The usual therapeutic dose is 20 to 30 mg daily in two to three divided doses.

Missed Dose
If a patient is taking *CO* Buspirone regularly and misses a dose, the missed dose should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the patient should go back to the regular dosing schedule.

Patients taking *CO* Buspirone should be advised against doubling doses.

Administration
CO Buspirone tablets are intended for oral administration.

OVERDOSAGE

Symptoms:
In clinical pharmacology trials, buspirone up to 400 mg/day was administered to healthy male volunteers. As this dose was approached, the following symptoms were observed in descending order of frequency: drowsiness, ataxia, nausea and vomiting, dizziness, clammy feeling, difficulty thinking, feeling "high", "rushing" sensation, gastric distress, headache, itching, miosis, hypotension, tremor, incoordination, insomnia and hallucinations. In a dose ranging study in acute psychotic patients, up to 2400 mg/day was administered. Dizziness, nausea and vomiting were the most common adverse effects. One patient developed extrapyramidal symptoms at 600 mg/day.

Treatment:
There is no specific antidote for buspirone. Management should, therefore, be symptomatic and supportive. Any patient suspected of having taken an overdose should be admitted to a hospital as soon as possible, and the stomach emptied by gastric lavage. Respiration, pulse and blood pressure should be monitored, as in all cases of drug overdosage. As with the management of intentional overdosage with any drug, the ingestion of multiple agents should be suspected. In six anuric patients, hemodialysis either had no effect on the pharmacokinetics of buspirone or decreased its clearance. The metabolite is partially removed by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Buspirone is a psychotropic drug with selective anxiolytic properties which belongs chemically to the class of compounds known as the azaspirodecanediones, not chemically or pharmacologically related to benzodiazepines, barbiturates, or other known psychotropic agents.

Buspirone shares some of the properties of the benzodiazepines and the neuroleptics, as well as demonstrating other pharmacological action.

Buspirone has an affinity for brain D_2-dopamine receptors, where it acts as an antagonist and agonist, and for the 5-HT_{1A} receptors where it acts as an agonist. Buspirone does not block the neuronal reuptake of monoamines and, on chronic administration, it does not lead to changes in receptor density in the models investigated. However, the mechanism of action of buspirone in man remains to be elucidated.

Pharmacodynamics

Buspirone attenuates punishment suppressed behavior in animals and exerts a taming effect, but is devoid of anticonvulsant and muscle relaxant properties and does not bind to the benzodiazepine/GABA receptor complex. Buspirone affects a variety of dopamine mediated biochemical and behavioral events, but it is free of cataleptic activity.

Pharmacokinetics

Absorption: Buspirone is rapidly absorbed in man and undergoes extensive first pass metabolism. Following oral administration, low peak plasma levels of unchanged drug, of 1 to 6 ng/mL were observed 40 to 90 minutes after a single 20 mg dose. In a number of studies performed in healthy volunteers, the mean half-life of buspirone ranged from 2 to 3 hours up to approximately 11 hours with considerable variation in individual values. Multiple dose studies suggest that steady state plasma levels were usually achieved within a few days.

The effects of food upon the bioavailability of buspirone tablets have been studied in eight subjects. They were given a 20 mg dose with or without food. The AUC and Cmax of unchanged buspirone increased by 84% and 116%, respectively. The total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone.

Distribution: In man, approximately 95% of buspirone is plasma protein bound. Other highly bound drugs e.g., phenytoin, propranolol and warfarin, are not displaced by buspirone from plasma protein binding *in vitro* at clinically relevant concentrations. However, *in vitro* binding studies show that buspirone does displace digoxin.

Metabolism: Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by Cytochrome P450 3A4 (CYP3A4) (see Warnings and Precautions, Significant

Interactions), producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinlypiperazine (1-PP). In animal models predictive of anxiolytic potential, 1-PP has about 25% or less of the activity of buspirone. Peak plasma levels of 1-PP have been found to be higher than those of its parent drug and its half-life to be approximately double that of unchanged buspirone.

Excretion: In a single dose study using ^{14}C-labelled buspirone, 29 to 63% of the dose was excreted in the urine within 24 hours, primarily as metabolites, while fecal excretion accounted for 18 to 38% of the dose.

Special Populations and Conditions

Pediatrics: No data available

Geriatrics: Clinical data found in a comparative trial with younger and elderly patients indicated that buspirone may be administered to patients aged 65 years or older without any special adjustment in dose and without the occurrence of unusual adverse age-related phenomena.

Gender: No significant differences in buspirone pharmacokinetics as a function of age and/or sex were found.

Race: No data available.

Hepatic Insufficiency: Buspirone had no effect on hepatic microsomal enzyme activity when administered to rats for 5 days. In man, the effect of buspirone on drug metabolism or concomitant drug disposition has not been studied. Buspirone clearance is reduced in patients with hepatic impairment.

Renal Insufficiency: Buspirone clearance is reduced in patients with impaired renal function.

Genetic Polymorphism: No data available.

STORAGE AND STABILITY

CO Buspirone tablets should be stored at controlled room temperature (15 - 30°C). Protect from light.

SPECIAL HANDLING INSTRUCTIONS

Not applicable**.**

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form:

CO Buspirone tablets are available in 2 strengths, namely 5 mg and 10 mg.

5 mg tablets:
Round, white, biconvex, compressed tablet scored on one side and embossed "ICN B21" on the other.

10 mg tablets:
White to off-white, modified rectangular-shaped, biconvex tablet with ">" on one side and "BU|10" on the other

Composition:
Each tablet contains either 5 mg or 10 mg of buspirone hydrochloride as the active (medicinal) ingredient.

The inactive ingredients are:
- colloidal silicon dioxide
- lactose
- magnesium stearate
- microcrystalline cellulose
- sodium starch glycolate

Packaging:

5 mg: Available in HDPE bottles of 100's and 500's.

10 mg: Available in HDPE bottles of 100's and 500's.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

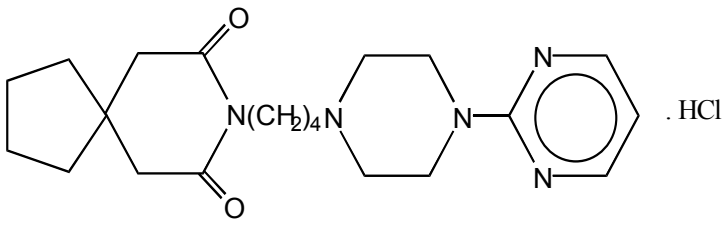
Proper name: Buspirone Hydrochloride, USP

Chemical name: 8-Azaspiro[4,5]decane-7,9-dione,8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl], monohydrochloride
Or
N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclopentanediacetamide monohydrochloride.

Molecular formula: $C_{21}H_{31}N_5O_2$. HCl

Molecular mass: 421.97

Structural formula:



Physicochemical properties: Buspirone hydrochloride is a white crystalline powder which is very soluble in water.

CLINICAL TRIALS

Bioequivalence parameter from a study comparing a Canadian Reference Product and the test product in healthy volunteers are summarized in the table below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
From measured data
Geometric Mean
Arithmetic Mean (CV%)

PARAMETER	TEST BUSTAB (ICN Canada)	REFERENCE BUSPAR (Bristol Canada)	RATIO OF MEANS
AUC_T (ng.hr/mL)	9.52 14.34 (99.52)	10.13 15.97 (104.54)	94.2
AUC_I (ng.hr/mL)	10.26 15.00 (96.71)	11.26 17.00 (99.78)	93.16
C_{max} (ng/mL)	3.22 5.19 (121.05)	3.49 5.78 (113.21)	92.7
T_{max} (hr)*	1.02 (77.64)	0.94 (55.27)	
$T_{1/2}$ (hr)*	2.75 (58.48)	2.72 (37.35)	

* The T_{max} (hr) and $T_{1/2}$ (hr) parameters are expressed as the arithmetic means.
The reference product, Buspar (Bristol Laboratories Canada) was purchased in Canada.

DETAILED PHARMACOLOGY

Buspirone is a chemically novel agent with a pharmacological profile that differs from those of presently available psychotropic drugs, while sharing a number of pharmacologic actions with both the benzodiazepines and the neuroleptics.

Buspirone, like the benzodiazepines, is active in the Geller and Vogel conflict tests in which it attentuates punishment suppressed behavior. In these procedures, doses as low as 0.5 mg/kg s.c. or p.o. were active in cynomolgous monkeys and rats, respectively. However, Ro 15-1788, the benzodiazepine antagonist, had no effect on the buspirone-elicited increased behavioral responding while it antagonized that elicited by the benzodiazepines. At somewhat higher doses, buspirone inhibited footshock-induced fighting behavior in mice and exerted a taming effect in aggressive rhesus monkeys. Both effects are characteristic of the benzodiazepines. In contrast, buspirone did not antagonize either chemical (pentylenetetrazol, bicuculline, strychnine, picrotoxin) or electroshock-induced convulsions, possessed minimal sedative activity and exerted minimal muscle relaxant activity.

Buspirone, like neuroleptics, decreased conditioned avoidance behavior, the minimal effective dose being approximately 1 mg/kg. At somewhat higher doses, buspirone protected against amphetamine-induced toxicity in aggregated mice and antagonized apomorphine-induced emesis in dogs. Intravenous buspirone (1.25 μg/kg) increased the firing rate of dopamine (DA) neurons both in the zona compacta of the substantia nigra and the ventral tegmentum. Under these conditions, buspirone was equipotent with haloperidol. When applied iontophoretically, buspirone had little effect per se but it blocked the DA or GABA-induced inhibition of DA cells. Classical antipsychotic drugs affect only the DA elicited responses. Buspirone also produced a dose-dependent increase in rat plasma prolactin levels (the minimal effective dose being approximately 0.5 mg/kg) and blocked the inhibitory effect of DA on prolactin secretion.

In contrast to the neuroleptics, buspirone did not induce catalepsy in doses up to 200 mg/kg and did not increase the density of 3-H-spiroperidol binding sites upon chronic administration.

Neurochemical studies revealed that buspirone was essentially devoid of *in vitro* interactions at the benzodiazepine/GABA receptor complex. Specifically, buspirone lacked affinity either for 3H-benzodiazepine binding sites (IC50 > 100 μM) or for GABA binding sites.

Furthermore, while in the presence of GABA or GABA agonists the affinity of the receptors increased for benzodiazepines, buspirone had no significant effect on either receptor affinity or density in concentrations ranging from 0.1 to 100 μM. The binding of a high affinity chloride ionophore radioligand also remained unaffected. However, under *in vitro* conditions, buspirone did enhance the binding of 3H-diazepam in the cortex and cerebellum, a finding which is opposite to that seen with most, but not all, benzodiazepines.

Buspirone, like the neuroleptics, inhibited the binding of 3H-spiperone and 3H-n-propylapomorphine (IC50 approximately 150 nM). Furthermore, the drug increased the rate of DA synthesis and turnover as shown by a significant increase in the level of striatal HVA and DOPAC. The latter effects were brought about by doses of 5 and 10 mg/kg buspirone. However, buspirone was a weak inhibitor of dopamine-stimulated adenylate cyclase.

Buspirone was shown to have weak or no affinity *in vitro* to cortical 5-HT_1 and 5-HT_2 receptors, although it did bind to hippocampal 5-HT_1 receptors (IC50 approximately 95 nM). More recently, buspirone has been identified as a 5-HT_{1A} receptor agonist. This interaction results in attenuated serotonergic neurotransmission brought about by decreased serotonin synthesis and release.

Buspirone was inactive at all other receptor sites studied, which included the alpha-1, alpha-2 and beta adrenergic, A_1 and A_2 adenosine, muscarinic cholinergic, H_1 and H_2 histamine, opiate, glycine and glutamate receptors. Buspirone did not inhibit the neuronal reuptake of DA, NE and 5-HT. The chronic administration of buspirone did not modify receptor density at alpha-1, alpha-2, beta or 5-HT_2 binding sites.

Based upon animal experiments, the abuse potential and dependence liability of buspirone seems to be minimal. The drug was not self-administered in monkeys trained to self-administer cocaine; it did not block convulsions precipitated in mice by the withdrawal of chronically administered

phenobarbital and caused no weight loss when stopped abruptly after repeated administration. Furthermore, buspirone did not share discriminative stimulus properties with either oxazepam or pentobarbital.

Buspirone is extensively metabolized and less than 1% of an oral dose is excreted unchanged. The major metabolites of buspirone are 5-hydroxybuspirone, which is pharmacologically essentially inactive, and its further oxidized derivatives and 1-(2-pyrimidinyl)-piperazine (1-PP) which is obtained by oxidative dealkylation. 1-PP is an active metabolite; it has anticonflict activity, and in contrast to buspirone, is highly effective at central alpha-2-adrenoceptors (IC50 approximately 25 nM) but virtually inactive at other binding sites.

MICROBIOLOGY
No data available.

TOXICOLOGY
Acute Toxicity

Species	Sex	Route	LD_{50} (95% Confidence Interval) mg/kg
Rat (Adult)	Males	Oral	265 (174 - 404)
Rat (Adult)	Males/Females	Oral	196 (152 - 252)
Rat (Newborn)	Males/Females	Oral	415 (332 - 520)
Mouse	Males	Oral	655 (529 - 811)
Dog	Males/Females	Oral	586 (371 - 925)
Monkey	Males/Females	Oral	356 (302 - 420)
Rat (Adult)	Males/Females	Intraperitoneal	136 (122 - 152)
Mouse	Males	Intraperitoneal	164 (145 - 185)
Mouse	Males	Intravenous	73.3 (66.6 - 80.6)
Monkey	Males/Females	Intravenous	54.3 (47.6 - 61.9)
Dog	Females	Intravenous Infusion	125.3 (lowest lethal dose - infused at 80 mg/kg/hr-30.8 mL/hr)

Signs of toxicity in all species included hypoactivity, salivation, tremors, ataxia, opisthotonos and clonic convulsions.

In the dog intravenous infusion test. 10 mg/kg/hr for a total of 59/mg/kg produced an increase in blood pressure and a slight increase in the ST segment of the EKG. At 40 and 80 mg/kg/hr, an increase in heart rate and T-wave amplitude was also observed. The animals at the higher doses died following convulsions.

Subacute Toxicity

Dog

In a two week dose ranging study, one male and one female dog per group received 73, 110 or 146 mg/kg buspirone orally immediately after feeding. Both high dose dogs died on day 5 following convulsions. The mid dose male died on day 11, probably due to acute gastric dilatation. Reddening of gastric mucosa was observed at necropsy in all three dogs that died.

Rat

In a three month study, groups of 15 males and 15 female rats were administered 0, 50, 100 and 200 mg/kg/day of buspirone in the diet. Reduced weight gain was observed in all treated groups, as well as slight but significant decreases in erythrocyte and serum protein values. A significant decrease in serum glucose levels was seen in the mid and high dose groups.

Monkey

In a three month study, 2 males and 2 females per group received 0, 37.5, 75 and 150 mg/kg of buspirone by gavage 3 hours after feeding. Hypoactivity, tremors and salivation were observed in all treated groups. Hypoactivity tended to increase with time. Other observations included catatonia in the mid dose group, ataxia in the high dose group, and general incoordination, in which the monkey would be in almost constant movement and unable to walk or grasp objects normally, in both mid and high dose groups.

Chronic Toxicity

Rat

In a 2 year study, buspirone was administered in the diet to groups of 70 male and 70 female rats at doses of 0, 48, 80 and 160 mg/kg/day. Food consumption and weight gain were reduced in the treated animals in a dose-related manner. Rapid respiration, tremors and tachycardia were observed in all treated groups, hypersensitivity in mid and high dose groups, and hunched, thin appearance and red or mucoid nasal discharge in the high dose group. Findings at necropsy included a dose-related incidence of pulmonary histiocytosis and some decrease in organ weights.

Mouse

A 78 week study was conducted with groups of 65 male and 65 female mice, who received buspirone 0, 50, 100 and 200 mg/kg/day in the diet.

Food intake was not affected, but decreased weight gain was observed in all treated groups. Necropsy findings included an increased incidence of amyloid deposition in some tissues of the high dose animals, particularly in the renal, gastrointestinal and testicular tissues of males. An increased incidence of focal testicular atrophy was also observed in high dose males.

Monkey

Groups of 4 male and 4 female Rhesus monkeys were given buspirone orally at doses of 0, 35, 62 and 110 mg/kg/day. After 23 days, buspirone doses were reduced to 25 mg/kg once daily, 25 mg/kg twice daily and 50 mg/kg twice daily, respectively, for the remainder of the one-year study.

One male in the mid dose and 4 males and 2 females in the high dose group died relatively early during the study (2 more died at the end). Slight to marked weight loss was seen in some of the monkeys that died. Prior to dose reduction, sedation was moderate at the low dose and marked at the mid and high dose. For the remainder of the study, slight to marked dose related sedation as well as intention tremors were observed in all treated groups. Mid and high dose monkeys also showed lack of responsiveness to stimuli and partial to total anorexia. Chewing on the cage or on the wrist was noted in high dose monkeys.

Some monkeys at the mid and high dose levels showed lower hemoglobin, hematocrit and alkaline phosphatase levels than controls, while in the high dose group, SGOT, and SGPT levels were slightly higher and serum cholesterol levels lower than in controls.

At necropsy, some changes in organ weights were observed, especially in the high dose group. Gross evidence of gastrointestinal irritation was found in all 7 monkeys that died during the study. A bloody diarrhea had been noted in 4 of the animals prior to death. One male monkey died at the end of the study with gross evidence of pericarditis and pleuritis. No distinct or consistent drug related histopathologic changes were found in this study.

Carcinogenicity

One two year combined carcinogenicity and toxicity study has been carried out in rats (see Chronic Toxicity for details). No evidence was found of a drug-related effect on mortality, incidence of palpable tissue masses, gross pathologic findings, organ weights or microscopically detected neoplasms.

Reproduction and Teratology

The potential effect of buspirone on the fertility and reproductive performance of the rat was assessed by mating treated female rats with non-treated males and vice versa. Groups of rats were given 9, 18, or 36 mg/kg/day of buspirone for 14 days prior to mating and continuing until 21 days post partum. The only finding was that pup weights were statistically lower at birth and during weaning of the offspring from both the male and female rats treated with 9, 18 or 36 mg/kg/day of buspirone. This was due to a more pronounced effect on pup weight in the litters with greater number of pups. The survival index for pups from highest dose female treated rats was reduced. The lactation index was reduced at 36 mg/kg dose level and the survival index was reduced when both parents were treated with buspirone.

There were no skeletal or visceral abnormalities or other findings indicating a teratogenic or embryotoxic effect in rats or rabbits treated during embryogenesis with doses of 9, 18 or 36 mg/kg/day. Administration of buspirone to the pregnant rat at 36 mg/kg/day or less during the last third of pregnancy and throughout the 3 week post-natal period revealed no evidence of any adverse effect on fetal development, birth weights, post-natal growth or survival.

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PART III: CONSUMER INFORMATION

_CO_ Buspirone
Buspirone HydrochlorideTablets

This leaflet is part III of a three-part "Product Monograph" published when *CO* Buspirone was approved for sale in Canada and is designed specifically for Consumers.
This leaflet is a summary and will not tell you everything about *CO* Buspirone. Contact your doctor or pharmacist if you have any questions about the drug

ABOUT THIS MEDICATION

What the medication is used for:
CO Buspirone is used for the temporary relief of excessive anxiety (worry).

What it does:
Buspirone affects behaviours which depend on a chemical messenger in the brain called dopamine.

When it should not be used:
Do not take *CO* Buspirone if you have experimented unusual or allergic reactions to buspirone hydrochloride or any other ingredients in this medication (see what the important non medicinal ingredients are).
Do not take *CO* Buspirone if you have serious liver or renal problem.

What the medicinal ingredient is:
Buspirone hydrochloride, USP

What the important nonmedicinal ingredients are:
CO Buspirone tablets contain: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate..

What dosage forms it comes in:
Tablet 5 mg and 10 mg

WARNINGS AND PRECAUTIONS

Taking Buspirone and Monoamine Oxidase Inhibitor (IMAO) antidepressants may cause high blood pressure. Therefore, you should avoid taking IMAO antidepressants while taking this medication (see interaction with this medication).

Movement disorders, trembling in hands, arms, legs, jaw, and face: rigidity may be noticed while taking *CO* Buspirone. Talk to your doctor if you experience any of the effects while taking this medication.

WARNINGS AND PRECAUTIONS CONTINUED

Buspirone may cause some people to become dizzy, lightheaded, drowsy, or less alert than they are normally. Make sure you know how you react to this medicine before you drive, use machines, or do anything else that could be dangerous if you are dizzy or are not alert.

BEFORE you take *CO* Buspirone talk to your doctor or pharmacist if you have any of the following conditions:

- Allergies: Tell you doctor if you have ever had any unusual or allergic reaction to buspirone. Inform your doctor if you are allergic to any other substances, such as foods, preservatives, or dyes.
- Pregnancy: Buspirone has not been studied in pregnant women. Therefore, if you are pregnant or plan to become pregnant inform your physician of your condition before taking the drug.
- Breast-feeding: It is not known if buspirone passes into the breast milk of humans.
- Children: Studies with buspirone have been done only in adult patients.
- Older adults: Buspirone has been studied in this age group and has not been shown to cause different side effects or problems in older people than it does in younger adults.
- Tell your doctor all the medication you are taking (see interaction with this medication).
- Other medical problems: the presence of other medical problems may affect the use of buspirone. Make sure you tell your doctor if you have any other medical problem, especially:
  - kidney disease, or
  - liver disease (the effects of buspirone may be increased, which may increase the chance of side effects).

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with *CO* Buspirone include:

- Cimetidine
- Diazepam
- Nefazodone, Erythromycin, Itraconazole, Diltiazem, Verapamil, Rifampicin
- Haloperidol
- Monoamine Oxidase Inhibitors (see Warnings and Precautions)
- Ketoconazole or Ritonavir, Dexamethasone or certain anticonvulsants (phenytoin, phenobarbital, carbamazepine).
- Phenytoin, Propranolol and Warfarin
- Trazodone

Other interactions that may occur with *CO* Buspirone include: food, grapefruit juice and alcohol. Avoid consuming alcohol and large amount of grapefruit juice.

CO Buspirone when taken with alcohol or medicines that slow down the nervous system, such as antihistamines or medicine for hay fever, other allergies, or colds, sedatives, tranquillizers, or sleeping medicine; prescription pain medicine or narcotics, barbiturates/medicine for seizures; muscle relaxants; or anesthetics, including some dental anesthetics, the chance of drowsiness may

increase. Therefore, you should avoid taking this medication with alcohol or other CNS depressants.

PROPER USE OF THIS MEDICATION

Take *CO* Buspirone only as directed by your doctor. DO NOT take more of it, DO NOT take it more often, and DO NOT take it for a longer time than your doctor ordered. To do so may increase the chances of unwanted effects.

After you start taking *CO* Buspirone, 1 or 2 weeks may pass before you feel the full effects of this medicine.

Usual dose:
Your doctor will decide the dose and duration of treatment. Do not change your dose unless directed by your doctor.

Adults: to start, 5 milligrams two or three times a day. Your doctor may adjust your dose depending on your needs, tolerance and condition to be treated.

Overdose:
If you or someone else may have taken an overdose of buspirone, get emergency help immediately. Some symptoms of an overdose are dizziness or drowsiness; stomach upset, including nausea or vomiting.

Missed Dose:
If you are taking *CO* Buspirone regularly and you miss a dose, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its needed effects, a medicine may cause some unwanted effects. Although, not all of these side effects may occur, if they do occur they may need medical attention.

Some commonly experienced side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, check with your doctor these side effects continue or are bothersome.

The most common adverse reactions are: dizziness, drowsiness, headache and nausea.

Some less common adverse reactions are: blurred vision, decreased concentration, dryness of mouth, cramps or stiffness, muscle pain, nightmares, ringing in ears, spasms, stomach upset, trouble sleeping, unusual tiredness or weakness and vivid dreams.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		**Talk with your doctor or pharmacist**		Stop taking drug and call your doctor or pharmacist
		Only if Severe	In all cases	
Rare	• chest pain			✓
	• confusion or mental depression			✓
	• fast or pounding heart beat			✓
	• muscle weakness			✓
	• numbness, tingling, pain or weakness in hands or feet			✓
	• sore throat or fever			✓
	• uncontrolled movements of the body			✓

This is not a complete list of side effects. For any unexpected effects while taking CO Buspirone*, contact your doctor or pharmacist.*

HOW TO STORE IT

Storage of *CO* Buspirone for proper storage of the tablets:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Valeant Canada Limited, at: 1-514-744-6792.

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