PRODUCT MONOGRAPH

PRBUSPIRONE - 5
PRBUSPIRONE - 10

Buspirone Hydrochloride Tablets USP

5 mg and 10 mg

ANXIOLYTIC

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THERAPEUTIC CLASSIFICATION

Anxiolytic

ACTION AND CLINICAL PHARMACOLOGY

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 attenuates punishment suppressed behaviour 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 behavioural events, but is free of cataleptic activity. 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.

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. Buspirone is metabolized primarily by oxidation, which *in vitro* has been shown to be mediated by Cytochrome P450 3A4 (CYP3A4) (see PRECAUTIONS, Significant Interactions), producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (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. 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. 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.

The effects of food upon the bioavailability of buspirone have been studied in eight subjects. They were given a 20 mg dose with or without food. The AUC and C_{max} 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.

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 as well as in patients with impaired renal function. No significant differences in buspirone pharmacokinetics as a function of age and/or sex were found.

A balanced, randomized, two-way, single-dose crossover study was conducted in 36 healthy, adult male volunteers in order to compare the bioavailability of BUSPIRONE 10 mg tablets to Buspar® 10 mg tablets. A summary of the pharmacokinetic parameters evaluated in the 35 subjects who completed the study are listed below:

Geometric Mean Arithmetic Mean (CV%)			
Parameter	**BUSPIRONE 2 x 10 mg**	**BUSPAR† 2 x 10 mg**	**% Buspirone Test/References**
AUC_T (ng•hr/mL)	2.99 6.43 (272)	3.27 5.70 (191)	91
AUC_I (ng•hr/mL)	3.47 6.88 (260)	3.71 6.09 (181)	94
C_{max} (ng/mL)	1.63 3.04 (240)	1.65 3.03 (190)	99
T_{max}* (hr)	0.66 (0.21)	0.72 (0.25)	-
$t_{1/2}$* (hr)	1.99 (0.73)	1.88 (0.67)	-
*These are arithmetic means (standard deviation) †Manufactured by Bristol Laboratories of Canada; purchased in Canada.			

INDICATIONS AND CLINICAL USE

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

The effectiveness of buspirone hydrochloride 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.

CONTRAINDICATIONS

BUSPIRONE (buspirone hydrochloride) is contraindicated in patients hypersensitive to buspirone hydrochloride or any ingredient in the formulation, including non-medicinal ingredients.

BUSPIRONE is contraindicated in patients with severe hepatic or severe renal impairment.

BUSPIRONE is contraindicated in patients treated with monoamine oxidase (MAO) inhibitors in the last 14 days, including methylene blue (intravenous dye) and linezolid (an antibiotic which is a reversible non-selective MAO inhibitor).

WARNINGS

MAO Inhibitors

The occurrence of elevated blood pressure in patients receiving both buspirone hydrochloride and a monoamine oxidase inhibitor (MAOI) has been reported. Therefore, it is recommended that buspirone should not be used within 14 days of treatment with an MAOI (see CONTRAINDICATIONS).

Serotonin Toxicity/Serotonin Syndrome

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with buspirone particularly during combined use with other serotonergic drugs (see DRUG INTERACTIONS)

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with BUSPIRONE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see DRUG INTERACTIONS). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Extrapyramidal Symptoms

Since buspirone can 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 (see PRECAUTIONS).

Convulsive Disorders

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

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 half-life of elimination. 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.

Use in Pregnancy, Lactation, Labor and Delivery

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.

PRECAUTIONS

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 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.

Significant 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.

Food
Food may decrease the extent of presystemic clearance of buspirone.

Monoamine Oxidase Inhibitors
Concomitant use of monoamine oxidase inhibitors and buspirone has been reported to cause an increased risk of serotonin syndrome/toxicity and elevated blood pressure. Therefore, concomitant use of these medications is not recommended (see WARNINGS).

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

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.

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).

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.

Serotonergic agents
The development of a potentially life-threatening serotonin syndrome/toxicity has been reported with SNRIs, SSRIs, and other serotonergic drugs, including buspirone, alone but particularly with concomitant use of other serotonergic drugs (including triptans) (see WARNINGS).
Seizures have been reported rarely in patients taking this combination.

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.

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.

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 C_{max} 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 increases in C_{max} 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.

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 C_{max} 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 C_{max} and a 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.

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 C_{max} 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.

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 C_{max} 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.

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 C_{max} and 89.6% decrease in AUC) and pharmacodynamic effects 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 increase in C_{max} and 9.2-fold increase in AUC). Patients receiving buspirone should be advised to avoid consuming large amounts of grapefruit juice.

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. 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 C_{max} (40%) and T_{max} (2-fold) of buspirone, but had minimal effect on AUC of buspirone.

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

Drug Abuse and Dependence
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.

Use in Patients with Impaired Hepatic or Renal Function
Since it is metabolized by the liver and excreted by the kidneys, buspirone should be used with caution in patients with a history of hepatic or renal impairment. It is contraindicated in patients with severe hepatic or renal impairment.

Use in Children
The safety and effectiveness of buspirone in individuals below the age of 18 years have not been established.

Use in the Elderly
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.

Neuroendocrine Effects
Single doses of 30 mg or higher of 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.

Long-Term Toxicity

Buspirone can bind to central serotonin and 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). 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.

ADVERSE REACTIONS

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.

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 cannot be determined.

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

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

Autonomic
Frequent: Dry mouth, sweating/clamminess, blurred vision, constipation.
Infrequent: Urinary frequency, retention and burning, flushing.

Cardiovascular
Frequent: Tachycardia/palpipations, chest pain.
Infrequent: Syncope, hypotension, hypertension.
Rare: Congestive heart failure, cerebrovascular accident, myocardial infarction, cardiomyopathy, bradycardia, EKG change.

Gastrointestinal
Frequent: Nausea, G.I. distress, diarrhea, vomiting.
Infrequent: Flatulence, increased appetite, anorexia, hypersalivation, rectal bleeding, irritable colon.
Rare: Burning tongue.

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

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

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

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

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

POST-MARKETING EXPERIENCE
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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms
In clinical pharmacology trials, buspirone hydrochloride 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.

DOSAGE AND ADMINISTRATION

BUSPIRONE (buspirone hydrochloride) dosage should be individually adjusted, according to tolerance and response.

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 or 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 or three divided doses.

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.

Availability BUSPIRONE 5 mg tablets: each white, pillow-shaped, biconvex tablet, scored and engraved “BU 5” on one side and “APO” on the other, contains 5 mg buspirone hydrochloride. Available in bottles of 100, 250, 500 and 1000.

BUSPIRONE 10 mg tablets: each white, pillow-shaped, biconvex tablet, scored and engraved “BU 10” on one side and “PRO” on the other, contains 10 mg buspirone hydrochloride. Available in bottles of 100, 250, 500 and 1000.

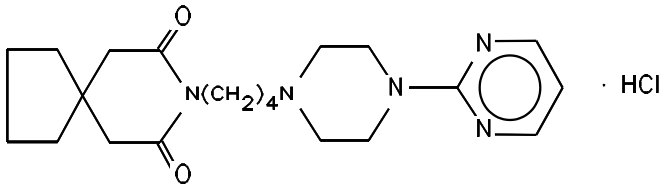
PHARMACEUTICAL INFORMATION

I Drug Substance

Common Name: Buspirone Hydrochloride

Chemical Names: 1) 8-Azaspiro[4,5]decane-7,9-dione,8-[4-[4-(2-pyrimidinyl)- 1-piperazinyl]butyl]-, monohydrochloride;
2) *N*-[4-[4-(2-Pyrimidinyl)-1-piperazinyl]butyl]-1,1-cyclo-pentanediacetamide monohydrochloride.

Structural Formula:



Molecular Formula: $C_{21}H_{31}N_5O_2$ HCl

Molecular Weight: 421.97

Description: Buspirone hydrochloride is a white to yellowish, crystalline, odourless powder which is very soluble in water and soluble in methanol. It is sparingly soluble in ethanol.

II Composition

BUSPIRONE (buspirone hydrochloride) tablets contain the following non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose, magnesium stearate and microcrystalline cellulose.

III Storage

BUSPIRONE tablets should be stored at room temperature (15°-30°C) in tight, light-resistant containers.

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 pharmacological actions with both the benzodiazepines and the neuroleptics.

Buspirone, like the benzodiazepines, is active in the Geller and Vogel conflict tests in which it attenuates punishment suppressed behaviours. 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 behavioural responding while it antagonized that elicited by the benzodiazepines. At somewhat higher doses, buspirone inhibited footshock-induced fighting behaviour 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 behaviour, 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 mcg/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 3H-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 (IC_{50} > 100 mcgM) 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 mcgM. 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 (IC_{50} approximately 150 nM). Furthermore, the drug increased the rate of DA synthesis and turnover as shown by a significant increase in the levels 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 (IC_{50} 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 α_1, α_2 and β 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 of α_1, α_2, β 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 α_2-adrenoceptors (IC_{50} approximately 25 nM) but virtually inactive at other binding sites.

TOXICOLOGY[1]

Acute Toxicity

Species	Sex	Route	LD_{50} (95% Confidence Interval) mg/Kg
Rat (Adult) Rat (Adult)	Males Males/Females	Oral Oral	265 (174-404) 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 females 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 numbers 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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