PRODUCT MONOGRAPH

PrMINT-BUSPIRONE

Buspirone Hydrochloride Tablets USP, 10 mg

ANXIOLYTIC

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PRODUCT MONOGRAPH

PrMINT-BUSPIRONE

Buspirone Hydrochloride Tablets USP, 10 mg

THERAPEUTIC CLASSIFICATION

Anxiolytic

ACTIONS AND CLINICAL PHARMACOLOGY

Buspirone is a psychotropic drug with anxiolytic properties which belongs chemically to the class of compounds known as the azaspirodecanediones.

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 remains to be fully 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, producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP). 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, but other highly bound drugs, e.g. phenytoin, propranolol and warfarin, are not displaced by buspirone from plasma protein *in vitro*. However, *in vitro* binding studies show that buspirone does displace digoxin.

The effect of food upon the bioavailability of buspirone was studied in 8 subjects. The area under the plasma concentration curve (AUC) and peak plasma concentration (C_{max}) of unchanged buspirone increased by 84% and 116% respectively when the drug was administered with food, but the total amount of buspirone immunoreactive material did not change. The significance of this finding is not known, but it could indicate that food may decrease the 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. The pharmacokinetics of buspirone in patients with hepatic or renal dysfunction, and in the elderly, has also not been clearly established.

MINT-BUSPIRONE (buspirone hydrochloride) 10 mg tablets have satisfied the criteria for a Biopharmaceutics Classification System (BCS)-based biowaiver in comparison to the respective strength of Apo-Buspirone (buspirone hydrochloride) tablets (Apotex Inc.).

INDICATIONS AND CLINICAL USE

MINT-BUSPIRONE (buspirone hydrochloride) is indicated for the short term symptomatic relief of excessive anxiety in patients with generalized anxiety disorder (psychoneurotic disorder).

Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. 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 in two of these trials with diazepam than with placebo. The adverse effect profiles of buspirone and diazepam in these clinical trials were, however, different.

CONTRAINDICATIONS

MINT-BUSPIRONE (buspirone hydrochloride) is contraindicated in patients hypersensitive to buspirone hydrochloride.

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

WARNINGS

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 MINT-BUSPIRONE (buspirone hydrochloride) should not be used concomitantly with an MAOI.

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).

Since the effects of buspirone have not been evaluated in patients with a history of convulsive disorders and since it lacks anticonvulsant activity in animals, buspirone is not recommended for patients with 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.

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 and Lactation

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.

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

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 increased the bioavailability of unchanged buspirone in healthy subjects, possibly due to a reduced first-pass effect.

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.

In a study in normal volunteers, no interaction of buspirone with amitriptyline was seen. A similar study with buspirone and diazepam showed an increase in the levels of nordiazepam.

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.

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.

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

In vitro, buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins. However, there has been one report of prolonged prothrombin time when buspirone was added to the regimen of a patient treated with warfarin. The patient was also chronically receiving phenytoin, phenobarbital, digoxin and Synthroid. *In vitro*, buspirone may displace less firmly bound drugs like digoxin. The clinical significance of this property is unknown.
There have been no reports to date of interference of buspirone with commonly employed clinical laboratory tests.

Drug Abuse and Dependence

Although 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.

Possible Concerns Related to Buspirone's Binding to Dopamine Receptors

Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g. dystonia, pseudo-parkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

ADVERSE REACTIONS

The most common adverse reactions encountered with buspirone are dizziness, headache, drowsiness and nausea. During premarketing clinical trials with buspirone, approximately 10% of the patients discontinued treatment due to an adverse event.

Adverse reactions reported include the following:

CNS: Dizziness, headache, drowsiness, lightheadedness, insomnia, fatigue, nervousness, decreased concentration, excitement, depression, confusion, nightmares/ vivid dreams, anger/hostility. Infrequently (<1%) depersonalization, noise intolerance, euphoria/ feeling high, dissociative reaction, fear, loss of interest, dysphoria, hallucinations, seizures, suicidal thoughts. Rarely, slurred speech, claustrophobia, cold intolerance, stupor, psychosis.

Neurologic: Paresthesia, weakness, incoordination, tremor, numbness. Infrequently, muscle cramps and spasms, rigid/stiff muscles, involuntary movements, akathisia, slowed reaction time. Rarely, tingling of limbs, stiff neck, rigidity of jaw, ataxia.

Autonomic: Dry mouth, sweating/clamminess, blurred vision, constipation. Infrequently, urinary frequency, retention and burning, flushing.

Cardiovascular: Tachycardia, chest pain, palpitations. Infrequently, syncope, hypotension, hypertension. Rarely, congestive heart failure, cerebrovascular accident, myocardial infarction, cardiomyopathy, bradycardia, ECG change.

Gastrointestinal: Nausea, G.I. distress, diarrhea, vomiting. Infrequently, flatulence, increased appetite, anorexia, hypersalivation, rectal bleeding, irritable colon. Rarely, burning tongue.

Respiratory: Nasal congestion. Infrequently, shortness of breath, chest congestion, difficulty breathing, hyperventilation. Rarely, epistaxis.

Endocrine: Infrequently, decreased and increased libido, weight gain, weight loss, menstrual irregularity/breakthrough bleeding. Rarely, delayed ejaculation, impotence, galactorrhea, amenorrhea, thyroid abnormality.

Allergic or Toxic: Skin rash, sore throat. Infrequently, edema/facial edema, pruritus, chills/fever. Rarely, photophobia, erythema, flu-like symptoms.

Clinical Laboratory: Infrequently, increases in liver enzymes. Rarely, eosinophilia, leukopenia, thrombocytopenia.

Miscellaneous: Tinnitus, muscle aches/pains. Infrequently, redness/itching of eyes, altered taste/smell, roaring sensation in head, malaise, easy bruising, dry skin, arthralgia, blisters, hair loss. Rarely, acne, thinning of nails, sore eyes, inner ear abnormality, pressure on eyes, nocturia, enuresis, hiccups, voice loss, alcohol abuse.

Post Introduction Clinical Experience

Post-marketing experience in the United States has shown an adverse experience profile similar to that given above. Additional reports have included rare occurrences of allergic reaction, cogwheel rigidity, dystonic reaction, ecchymosis, emotional lability and tunnel vision. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to buspirone treatment has not been determined.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

MINT-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.

<u>Elderly Patients</u>

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.

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

PHARMACEUTICAL INFORMATION

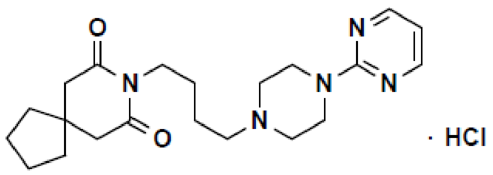
Drug Substance

Proper 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-cyclopentanediacetamide monohydrochloride.

Structural Formula:



Molecular Formula: $C_{21}H_{31}N_5O_2HCl$

Molecular Weight: 421.96 g/mol

Physicochemical Properties

White crystalline powder, very soluble in water; freely soluble in methanol and in methylene chloride; sparingly soluble in ethanol and in acetonitrile, practically insoluble in ethyl acetate hexanes.

Stability and Storage Recommendations

MINT-BUSPIRONE tablets should be stored at 15-30°C. Store in tight, light-resistant containers.

AVAILABILITY OF DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form	Tablet
Strength	10 mg
Description	White to off white, round, flat faced bevelled edge tablets, debossed with “245” on one side and “U" on either side of a scoreline on the other side.
Composition	Anhydrous lactose, microcrystalline cellulose, sodium starch glycolate Type A, colloidal silicon dioxide and magnesium stearate.
Packaging	HDPE Bottle pack of 100’s and 500’s count tablets.

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 attenuates punishment suppressed behaviours. In these procedures, doses as low as 0.5 mg/kg s.c. or p.o. were active in cynomolgus monkeys and rats, respectively. However, Ro 15-1788, the benzodiazepine antagonist, had no effect on the buspirone-elicited increased behavioral response 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 mcM) 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 mcM. The binding of a high affinity chloride ionophore radioligand also remained unaffected. However, under *in vivo* 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

Acute Toxicity

Species	Sex	Route	LD_{50} (95% Confidence Interval) mg/kg
Rat (Adult) Rat (Adult)	Male Male/Female	Oral Oral	265 (174-404) 196 (152-252)
Rat (Newborn)	Male/Female	Oral	415 (332-520)
Mouse	Male	Oral	655 (529-811)
Dog	Male/Female	Oral	586 (371-925)
Monkey	Male/Female	Oral	356 (302-420)
Rat (Adult)	Male/Female	i.p.	136 (122-152)
Mouse	Male	i.p.	164 (145-185)
Mouse	Male	i.v.	73.3 (66.6-80.6)
Monkey	Male/Female	i.v.	54.3 (47.6-61.9)
Dog	Female	i.v. 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 ECG. 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 decreases 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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Clinical

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