

Data Sheet

PACIFIC BUSPIRONE

5mg & 10mg tablets

Buspirone Hydrochloride

Presentation

5mg Tablets: Buspirone hydrochloride 5mg is a white, round tablet with "BR 5" embossed on one side and "G" on the other.

10mg Tablets: Buspirone hydrochloride 10mg is a white, capsule shaped tablet embossed "BR (breakline) 10" on one side and "G" on the other.

Uses

Actions

Buspirone hydrochloride represents a distinctly different chemical and pharmacologic class of psychotropic agent and has shown selective anxiolytic activity. It is not related to the benzodiazepines or other known anxiolytic agents. In contrast to the benzodiazepines, buspirone elicits its antianxiety effects without sedation, muscle relaxation, or compromise in mental alertness. In controlled clinical studies at comparable anxiolytic doses, buspirone produces significantly less sedation (drowsiness and/or fatigue) than either diazepam or clorazepate. It produces significantly less functional impairment (e.g. less impairment of motor vehicle driving skills) than either diazepam or lorazepam and does not differ from placebo.

The exact mechanism of buspirone's anxiolytic action in man is not fully understood, however, it differs from that of the benzodiazepines. *In vitro* preclinical studies have shown that buspirone has a high affinity for serotonin (5-HT_{1A}) receptors. Buspirone does not appear to interact directly with either the benzodiazepine or GABA receptors *in vitro* when tested in preclinical models. However, buspirone may have indirect effects on neurotransmitter receptor systems, including benzodiazepines, GABA and dopamine receptors. With respect to dopamine, buspirone appears to act as a presynaptic dopamine antagonist.

Pharmacokinetics

In man, buspirone hydrochloride is rapidly absorbed, reaching peak plasma levels 60 to 90 minutes after dosing. Mean peak plasma concentrations of 0.9, 1.7 and 3.2ng/mL were observed at doses of 10, 20, and 40mg, respectively; thus indicating the plasma concentration of buspirone hydrochloride is proportional to the administered dose.

The effects of food upon the bioavailability of buspirone tablets have been studied in eight subjects. They were given a 20mg 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 (see Dosage and Administration).

Buspirone is approximately 95% bound by human plasma proteins.

Half-life values observed in healthy volunteers ranged from 2 to 33 hours. Mean half-life values observed in healthy volunteers in the 14 studies conducted to date ranged from 2 to 11 hours. Women tended to have slightly but not statistically significantly longer half-life values than men.

After a single oral dose of ¹⁴C-buspirone in four subjects, excretion of radioactivity in urine accounted for 29 to 63% of the dose, the majority occurring within 24 hours of dosing and was composed primarily of metabolites; faecal excretion accounted for 18 to 38% of the dose.

Buspirone is metabolised primarily by oxidation, which *in vitro* has been shown to be mediated by Cytochrome P450 3A4 (CYP3A4). Several hydroxylated derivatives of buspirone are produced along with 1-pyrimidinylpiperazine (IPP). The latter is approximately one-fourth as active as buspirone in animal models predictive of anxiolytic activity.

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.

Indications

Buspirone hydrochloride is indicated for the management of anxiety disorders or the short-term relief of symptoms of anxiety with or without accompanying depression. The diagnosis of patients studied in controlled clinical trials of buspirone corresponds to the Generalised Anxiety Disorder of the WHO classification as described below:

Generalised, persistent anxiety is manifested by symptoms from three of the following four categories:

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

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

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

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

The anxious mood has been continuous for at least one month. The ordinary anxiety and tension associated with the stress of everyday life usually does not require treatment with an anxiolytic agent.

Controlled clinical studies of buspirone have been limited to six months.

Dosage and Administration

The usual starting dose is 5mg given three times daily. This may be titrated according to the needs of the patient and the daily dose increased by 5mg increments every two or three days depending upon the therapeutic response to a maximum daily dose of 60mg. After dosage titration the usual daily dose will be 20 to 30mg per day in divided doses.

Food increases the bioavailability of buspirone. Buspirone should be taken at the same time each day and consistently with or without food (see Pharmacokinetics).

If buspirone is given with a potent inhibitor of CYP3A4 such as itraconazole or nefazodone, the initial dose of buspirone should be reduced and titrated based on clinical assessment (see Interactions).

Grapefruit juice increases the plasma concentrations of buspirone. Patients taking buspirone should avoid consuming grapefruit juice (see Interactions).

The dose should be reduced in renal or hepatic impairment but buspirone should not be used in patients with severe renal or hepatic impairment (see Warnings & Precautions).

Contraindications

Buspirone hydrochloride is contraindicated in patients hypersensitive to buspirone hydrochloride or any of the inactive ingredients.

Warnings and Precautions

Monoamine Oxidase Inhibitors:

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

Convulsive Disorder:

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

Renal impairment:

Buspirone should be used cautiously in patients with renal disease. Since buspirone is excreted by the kidneys the dose should be reduced in patients with renal impairment but administration of buspirone to patients with severe renal impairment cannot be recommended.

Hepatic impairment:

Buspirone should be used cautiously, at reduced doses, in patients with impaired hepatic function. Buspirone clearance is reduced in patients with hepatic cirrhosis. In one study, a single 20mg oral dose led to 16 fold and 13 fold increases in mean peak buspirone blood levels and mean peak AUC respectively in cirrhotic patients compared to normal volunteers. Administration of buspirone to patients with severe hepatic impairment is not recommended.

Interference with Cognitive and Motor Performance:

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

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

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

Because buspirone does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with buspirone, it is advisable to withdraw these drugs gradually, especially in patients who have been using a CNS-depressant drug chronically.

Rebound or withdrawal symptoms from benzodiazepines and other sedative/hypnotic drugs may occur over varying periods, depending in part on the type of drug and its effective half-life of elimination, and may include any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally seizures.

Post-marketing placebo-controlled clinical studies have been performed to assess the safety and efficacy of switching benzodiazepine-treated patients to buspirone therapy without a benzodiazepine withdrawal/washout period. Results of these studies and of general post-marketing clinical experience have shown that, in patients in whom a benzodiazepine washout period is not feasible, gradual benzodiazepine taper/withdrawal may be overlapped by buspirone therapy over a few weeks in anxious patients requiring continued therapy. Buspirone should not, however, be used to detoxify patients addicted to benzodiazepines.

Long-Term Toxicity:

Buspirone can bind to central serotonin and dopamine receptors and increases noradrenergic activity, but differs chemically and pharmacologically from traditional central nervous system agents. Because its mechanism of action is not fully elucidated, long-term toxicity in the CNS or other organ systems cannot be predicted.

Laboratory Tests:

Laboratory tests are not required in otherwise healthy patients.

Carcinogenesis and Mutagenesis:

No evidence of any carcinogenic potential of buspirone hydrochloride was observed during either a 24-month study in rats (at approximately 133 times the human oral dose) or an 18 month study in mice (at approximately 167 times the human oral dose).

With or without metabolic activation, buspirone did not induce point mutations *in vitro* when tested using *Salmonella typhimurium* (Ames Test) or mouse lymphoma L5178YTK⁺ cell cultures. DNA damage was not observed with buspirone using *in vitro* Wi-38 human cells, with and without metabolic activation. Chromosomal aberrations or abnormalities did not occur in bone marrow cells of mice given one or five daily doses of buspirone.

Use in Pregnancy:

Category B1.

Reproduction studies performed in rats and rabbits (at approximately 30 times the maximum recommended human dose) have revealed no evidence of impaired fertility or harm to the foetus due to buspirone hydrochloride.

There are however, no adequate and well-controlled studies in pregnant women. Therefore, use of buspirone during pregnancy should be initiated or continued only if in the opinion of the attending physician the benefit outweighs the potential risk.

Labour and Delivery:

The effect of buspirone hydrochloride on labour and delivery is unknown.

Breast Feeding:

The extent of excretion in human milk of buspirone or its metabolites is not known. In rats, buspirone and its metabolites are excreted in milk. Therefore, buspirone should be administered to a woman who is breast feeding only if in the opinion of the attending physician the benefit to the mother outweighs the potential risk to the breastfed infant.

Paediatric Use:

Safety and effectiveness of buspirone hydrochloride in children below the age of 18 years have not been established.

Use in the Elderly:

The pharmacokinetics of buspirone have been examined in groups of young (aged 21-39 years) and elderly (over 65 years) healthy male and female subjects. After either a single dose of buspirone or after dosing for five days, no significant effects of either age or gender on buspirone pharmacokinetics were observed. These data do not support a change in dosage regimen based on age or sex of the patient.

Adverse Effects

Side effects to buspirone hydrochloride, 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 hydrochloride were compared with patients receiving placebo, dizziness, headache, nervousness, lightheadedness, nausea, excitement and sweating/clamminess were only the side effects occurring with greater frequency ($P < 0.1$) in the buspirone group than in the placebo group.

Discontinuations in Placebo-Controlled Trials:

Approximately 10% of the 2200 anxious patients who participated in 3 to 4 week controlled clinical efficacy trials of buspirone in anxiety disorders 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.

Premarketing - All Studies:

This section reports all adverse events occurring at a frequency of 1% or greater in 3004 subjects who took multiple doses of buspirone in the dose range for which buspirone is being recommended (i.e. the modal daily dose of buspirone fell between 10 and 30mg for 70% of the patients studied) and for whom safety data were systematically collected. The conditions and duration of exposure to buspirone varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship of the adverse event to buspirone treatment cannot be determined.

Adverse Drug Events Reported During Premarketing Evaluation

Body System	Premarketing	
	n=3004	%
Cardiovascular		
Tachycardia/palpitations	72	2.4
Chest pain	38	1.3
CNS		
Dizziness	392	13.5
Drowsiness	307	10.2
Nervousness/excitement	217	7.2
Lightheadedness	197	6.6

Insomnia	191	6.4
Decreased concentration/ abnormal thinking	82	2.7
Depression	60	2.0
Confusion	52	1.7
Dream disturbances	43	1.4
Anger/hostility	36	1.2
EENT		
Blurred vision	65	2.2
Nasal congestion	34	1.1
Sore throat	32	1.1
Tinnitus	30	1.0
Gastrointestinal		
Nausea	294	9.8
Abdominal distress	145	4.8
Dry mouth	111	3.7
Diarrhea	106	3.5
Constipation	58	1.9
Vomiting	55	1.8
Musculoskeletal		
Musculoskeletal aches/pain	77	2.6
Neurological		
Paraesthesia/numbness	131	4.4
Incoordination	58	1.9
Tremor	35	1.2
Skin		
Rash	34	1.1
Miscellaneous		
Headache	340	11.3
Fatigue/weakness	239	8.0

This table includes only those adverse events which occurred at a frequency of 1% or higher during premarketing testing.

Spontaneous Reports:

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: Extra pyramidal 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 galactorrhoea.

Drug Abuse and Dependence:

Based on human and animal studies, buspirone hydrochloride shows no potential for drug abuse and dependence. Two double-blind clinical studies have been conducted using human volunteers with a history of recreational drug usage. In neither study were subjects able to distinguish between buspirone and placebo, whereas they reported a statistically significant preference for the positive controls, methaqualone and diazepam. Lack of potential for buspirone abuse was also demonstrated in several animal models: lack of drug self-administration in monkeys, failure to mitigate withdrawal signs in barbiturate dependent mice and failure to train rats to recognise interoceptive cues associated with buspirone.

Dependence:

No withdrawal-type reactions have been reported with buspirone hydrochloride therapy.

Abrupt withdrawal of buspirone hydrochloride following chronic administration in the rat did not result in the loss of body weight commonly observed with substances that cause physical dependence.

Although studies have shown that buspirone is not associated with physical dependence or drug-seeking behaviour, it is difficult to predict from experiments the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g. development of tolerance, incrementation of dose, drug-seeking behaviour).

Interactions

Other CNS Drugs: The concomitant use of buspirone with other CNS-active drugs should be approached with caution (see Warnings & Precautions).

MAO Inhibitors: There have been rare occurrences of elevated blood pressure when buspirone was added to a regimen including an MAOI. Therefore buspirone should not be used concomitantly with an MAOI.

SSRIs: Experience with the combination of buspirone and selective serotonin reuptake inhibitor (SSRI) antidepressants includes several clinical studies and more than 300,000 patients in clinical practice. Overall, there have been no major safety problems. Seizures have been reported rarely in patients taking buspirone and SSRIs.

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

Trazodone: (Not marketed in Australasia) It has been reported that the concomitant use of trazodone hydrochloride and buspirone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a study attempting to replicate this finding, no interactive effect on hepatic transaminases was identified.

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. Other substances that inhibit CYP3A4, such as ketoconazole or ritonavir, may inhibit buspirone metabolism and increase plasma concentrations of buspirone. Consequently, if buspirone is to be used in combination with a potent inhibitor of CYP3A4, a low dose of buspirone (see below for specific dosage recommendations) used cautiously, is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Nefazodone: The coadministration of buspirone (2.5 or 5 mg twice a day) and nefazodone (250 mg twice a day 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 twice a day doses of buspirone, slight increases in AUC were observed for nefazodone (23%) and its metabolites hydroxynefazodone (17%) and mCPP (9%). Slight increases in C_{max} were observed for nefazodone (9%) and its metabolite HO-NEF (11%). The side effect profile for subjects receiving buspirone 2.5 mg, twice a day and nefazodone 250 mg twice a day was similar to that for subjects receiving either drug alone. Subjects receiving buspirone 5 mg twice a day and nefazodone 250 mg twice a day experienced side effects such as lightheadedness, asthenia, dizziness and somnolence. It is recommended that the dose of buspirone be lowered (e.g. 2.5 mg once a day) when coadministered 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. 2.5mg twice a day) 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 once a day) 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 (10mg as a single dose) with diltiazem (60mg three times a day) increased plasma buspirone concentrations. The AUC and C_{max} of buspirone were increased 5.5-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 (10mg as a single dose) with verapamil (80mg three times a day) 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 (10mg as a single dose) with rifampicin (600mg/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.

Other inducers of CYP3A4: Substances that induce CYP3A4, such as dexamethasone, or certain anticonvulsants (phenytoin, phenobarbital, carbamazepine), may increase the rate of buspirone metabolism. Consequently 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), but had minimal effect on AUC of buspirone.

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 increased 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.

Alcohol Interactions: Buspirone hydrochloride does not significantly augment the depressant effect of alcohol. In comparative studies which tested psychomotor function, buspirone alone or in combination with alcohol showed significantly less impairment in psychomotor functions than either diazepam or lorazepam when each drug was administered alone or in combination with alcohol. However, it is prudent to avoid concomitant use of buspirone and alcohol.

Food: Food increases the bioavailability of unchanged buspirone in healthy subjects, possibly due to a reduced first-pass effect. [Uses - Pharmacokinetics]

As grapefruit juice is an inhibitor of CYP3A4, eating grapefruit or drinking the juice should be avoided during treatment with buspirone. In a study in healthy volunteers, coadministration of buspirone (10mg as a single dose) with double-strength grapefruit juice (200mL double-strength three times daily for 2 days) increased plasma buspirone concentrations (4.3-fold increase in C_{max} and 9.2-fold increase in AUC. [See Interactions - Potential Interaction with Drugs That Inhibit Cytochrome P450 3A4 (CYP3A4)]

Drug/Laboratory Test Interactions: There have been no reports of interference of buspirone hydrochloride with commonly employed clinical laboratory tests.

Overdosage

Signs and Symptoms: The maximum tolerated dose of buspirone hydrochloride is 375mg per day in healthy normal subjects. Death in humans by deliberate or accidental overdosage has not been observed with buspirone. As the maximum dose levels were reached, the

following symptoms were most commonly observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Animal Oral LD₅₀ Values: The oral LD₅₀ values for buspirone are 655 mg/kg in mice, 196 mg/kg in rats, 586 mg/kg in dogs, and 356 mg/kg in monkeys. These doses are several hundred multiples of the recommended human daily dose.

Treatment: General symptomatic and supportive measures should be administered along with immediate gastric lavage. Respiration, pulse and blood pressure should be monitored in all cases of overdose. As with the management of intentional overdosing with any drug the ingestion of multiple agents should be suspected. There is no specific antidote known for buspirone hydrochloride. Buspirone is not removed by haemodialysis; the metabolite 1-PP is partially removed by haemodialysis.

Pharmaceutical Precautions

Store below 25°C. Protect from light. Keep out of reach of children.

Medicine Classification

Prescription Medicine

Package Quantities

Bottles of 100 tablets

Further Information

Information for Patients: To assure the safe and effective use of buspirone hydrochloride, the following instructions should be given to patients by the physician:

1. Inform your physician about any medications, whether prescription or nonprescription, that you are now taking or planning to take during your treatment with buspirone hydrochloride.
2. Inform your physician if you are planning to become pregnant, or if you become pregnant while you are taking buspirone hydrochloride.
3. Inform your physician if you are breast feeding an infant.
4. Until you experience how this medication affects you and are sure that it causes no adverse effect, do not drive a vehicle or operate potentially dangerous machinery.
5. You must take your dose of buspirone the same way each time. If you begin your dosing with food, continue to take your buspirone with food. If you begin your dosing without food, continue taking your buspirone without food.
6. Do not take your buspirone with grapefruit juice.

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