PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]JAMP Buspirone

Buspirone Hydrochloride Tablets USP

Tablets, 10 mg, Oral

Anxiolytic

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Date of Initial Authorization:
December 18, 2020

Date of Revision:
February 10, 2023

Submission Control Number: 267286

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JAMP Buspirone (buspirone hydrochloride) is indicated for:

- 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.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Buspirone has not been systematically evaluated in geriatric 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 (See 7.1.4 Geriatrics).

Long-term use of JAMP Buspirone should be avoided in geriatric patients. Enhanced monitoring is recommended (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures; 4 .DOSAGE AND ADMINISTRATION, Dosing Considerations).

2 CONTRAINDICATIONS

JAMP Buspirone (buspirone hydrochloride) is contraindicated in patients:

- hypersensitive to buspirone hydrochloride or any ingredient in the formulation, including non- medicinal ingredients.
- with severe hepatic or severe renal impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; 7 WARNINGS AND PRECAUTIONS, Renal).
- 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)(see 9.4 Drug-Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Addiction, Abuse and Misuse

The use of benzodiazepines, including JAMP Buspirone, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing JAMP Buspirone
- Monitor all patients regularly for the development of these behaviours or conditions.
- JAMP Buspirone should be stored securely to avoid theft or misuse.

Withdrawal

Benzodiazepines, like JAMP Buspirone, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of JAMP Buspirone.
- Terminate treatment with JAMP Buspirone by gradually tapering the dosage schedule under close monitoring. (see 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant Use with Opioids

Concomitant use of JAMP Buspirone and opioids may result in profound sedation, respiratory depression, coma and death (see 7 WARNINGS AND PRECAUTIONS, General, Concomitant Use with Opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- JAMP Buspirone (buspirone hydrochloride) dosage should be individually adjusted, according to tolerance and response.
- JAMP Buspirone should always be prescribed at the lowest effective dose for the shortest duration possible.
- JAMP Buspirone can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; 4 WARNINGS AND PRECAUTIONS,

Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.

- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient eperiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see 7 WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of JAMP Buspirone should be avoided in geriatric patients. Enhanced monitoring is recommended.

4.2 Recommended Dose and Dosage Adjustment

The recommended initial dose is 5 mg two to three times daily. This may be titrated according to the needs of the patient and the daily dose increased by 5 mg increments every two 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.

Pediatric Patients: Health Canada has not authorized an indication for pediatric use.

Geriatric Patients: It is recommended that the maximum daily dose should not exceed 30 mg for a duration not exceeding 4 weeks (see 7.1.4 Geriatrics).

Renal and hepatic impairment: 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. If buspirone is administered to patients with compromised hepatic or renal function, careful monitoring will be required together with appropriate dosage adjustment (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic; Renal).

4.5 Missed Dose

IF A DOSE IS MISSED, INFORM THE PATIENT TO TAKE THE NEXT DOSE AT THE USUAL TIME.

5 OVERDOSAGE

Symptoms

Symptoms of overdosage may include: drowsiness, ataxia, nausea and vomiting, dizziness, clammy feeling, difficulty thinking, feeling "high", "rushing" sensation, gastric distress, headache, itching, miosis, hypotension, tremor, incoordination, insomnia, hallucinations and extrapyramidal symptoms.

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablets, 10 mg	anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Description

JAMP Buspirone 10 mg tablets: White to off-white, flat faced, capsule shaped tablet, scored on one side and debossed with "BU 10" on other side.

Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Concomitant Use with Opioids

Concomitant use of benzodiazepines, including JAMP Buspirone, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant Use with Opioids; 9.1 Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with benzodiazepines.

If a decision is made to prescribe JAMP Buspirone concomitantly with opioids, prescribe the

lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of JAMP Buspirone than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking JAMP Buspirone, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see 5 OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when Jamp Buspirone is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

MAO Inhibitors: The occurrence of elevated blood pressure and serotonin syndrome/toxicity 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 2 CONTRAINDICATIONS).

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.

Sensitivity/Resistance: JAMP Buspirone Tablet contains lactose. Patients with rare hereditary problems of glucose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product.

Dependence/Tolerance

Despite preliminary animal and human investigations suggesting that buspirone may be significantly devoid of potential for producing physical or psychological dependence, 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 of benzodiazepines, such as JAMP Buspirone, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of

psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with JAMP Buspirone with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing JAMP Buspirone. In individuals prone to substance use disorder, JAMP Buspirone should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- JAMP Buspirone should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

Withdrawal

Benzodiazepines, such as JAMP Buspirone, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses.

The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration – should be terminated by gradually tapering the dosage schedule under close monitoring.

- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.

Patients experiencing withdrawal symptoms should seek immediate medical attention. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; 4 DOSAGE AND ADMINISTRATION, Dosing Considerations)

Driving and Operating Machinery

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.

Endocrine and Metabolism

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.

Falls and Fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), geriatric or debilitated patients

Hepatic/Biliary/Pancreatic/Renal

Since it is metabolized by the liver, buspirone should be used with caution in patients with a history of hepatic impairment. It is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS, 4.2 Recommended Dose and Dosage Adjustment, Renal and hepatic impairment).

Neurologic

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

Long-Term Toxicity: Buspirone can bind to central serotonin and dopamine receptors. A question has been raised about 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.

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 9.4 Drug-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 JAMP BUSPIRONE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9.4 Drug-Drug Interactions). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Renal

Since it is excreted by the kidneys, buspirone should be used with caution in patients with a history of renal impairment. It is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS, 4.2 Recommended Dose and Dosage Adjustment, Renal and hepatic impairment).

Reproductive Health: Female and Male Potential

Fertility: Data from preclinical studies does not suggest that buspirone would be associated with an increased risk of reduced fertility (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

Teratogenic Risk: There are no adequate and well-controlled studies of buspirone in pregnant women. However, based on animal studies, there is no evidence that buspirone has a teratogenic or embryotoxic effect (see 7.1.1 Pregnant Women, 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of buspirone during pregnancy has not been established and, therefore, it should not be used in women of childbearing potential, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus.

The effect of buspirone on labor and delivery is unknown.

7.1.2 Breast-feeding

The safety of buspirone during lactation has not been established and, therefore, it should not be used in nursing mothers, unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the baby. Buspirone and its metabolites are excreted in milk in rats. The extent of excretion in human milk has not yet been determined. Precaution should be exercised because many drugs can be excreted in human milk.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Buspirone has not been systematically evaluated in geriatric 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**.**

Long-term use of JAMP Buspirone should be avoided in geriatric or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed

in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Commonly Observed: When patients receiving buspirone were compared with patients receiving placebo, dizziness, headache, nervousness, light headedness, 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.

System Organ Class	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Infrequent	Eosinophilia, leukopenia, thrombocytopenia
Cardiac disorder	Frequent	Tachycardia/palpitations, chest pain
	Infrequent	Syncope
	Rare	Congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia
Ear disorders	Frequent	Tinnitus
	Infrequent	noise intolerance
	Rare	Inner ear abnormality
Eye disorders	Frequent	blurred vision
	Infrequent	Redness/itching of eyes
	Rare	sore eyes, pressure on eyes, photophobia

System Organ Class	Frequency	Adverse Reactions
Gastrointestinal disorders	Frequent	Dry mouth, constipation, nausea, G.I. distress, diarrhea, vomiting
	Infrequent	Flatulence, hypersalivation, rectal bleeding, irritable colon
	Rare	Burning tongue, hiccups
General disorders and administration site conditions	Frequent	Fatigue, weakness
	Infrequent	burning, malaise, slowed reaction time, Edema/facial edema, chills/fever
	Rare	cold intolerance, Flu-Like Symptoms
Investigations	Frequent	Weight gain, weight loss
	Infrequent	Increases in liver enzymes
	Rare	Eosinophilia, leukopenia, thrombocytopenia, EKG Change
Metabolism and nutrition disorders	Frequent	Weight gain, weight loss
	Infrequent	increased appetite and anorexia
	Rare	Thyroid abnormality
Musculoskeletal and connective tissue disorders	Frequent	muscle aches/pains
	Infrequent	Arthralgia, Muscle cramps and spasms, rigid/stiff muscles
	Rare	Stiff neck, rigidity of jaw
Renal and urinary disorders	Infrequent	Urinary frequency, urinary retention, urinary burning
	Rare	nocturia, enuresis
Reproductive system and breast disorders	Frequent	Decreased and increased libido, menstrual irregularity/breakthrough bleeding
	Rare	Delayed ejaculation, impotence, galactorrhea, amenorrhea
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, sore throat
	Infrequent	Shortness of breath, chest congestion, hyperventilation
	Rare	Epistaxis, voice loss

System Organ Class	Frequency	Adverse Reactions
Skin and subcutaneous tissue disorders	Frequent	Sweating/clamminess, skin rash
	Infrequent	Easy bruising, dry skin, blisters, hair loss, pruritus
	Rare	Acne, thinning of nails, erythema
Vascular disorders	Infrequent	Flushing, hypotension, hypertension
	Rare	Cerebrovascular accident

8.5 Post-Market Adverse Reactions

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

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

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

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), geriatric and debilitated patients.

Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as JAMP BUSPIRONE. Severe and life-threatening symptoms have been reported. (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; 7 WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

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

9 DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of JAMP Buspirone and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see 7 WARNINGS AND PRECAUTIONS, General, Risks from Concomitant Use with Opioids)

9.3 Drug-Behavioural 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.

9.4 Drug-Drug Interactions

Table 3 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Amitriptyline	CT	↔ Buspirone ↔ Amitriptyline	In a study in normal volunteers, no interaction of buspirone with amitriptyline was seen.
CNS active drugs	T		The concomitant use of buspirone with other CNS active drugs should be approached with caution (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Serotonin Syndrome).

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Diazepam	CT	↔ Diazepam ↑ Nordiazepam	After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (Cmax, AUC, and Cmin) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.
Haloperidol	CT	↑ Haloperidol	In another study in normal volunteers, concomitant administration of buspirone and haloperidol resulted in increased serum haloperidol concentrations. The clinical significance of this finding is not clear.
Monoamine Oxidase Inhibitors	C	↑ serotonin syndrome/toxicity ↑ blood pressure	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, it is recommended that buspirone should not be used within 14 days of treatment with an MAOI (see 2 CONTRAINDICATIONS).

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Protein Binding	T	↑Prothrombin time	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 aspiri desipramine, diazepam, flurazepar ibuprofen, propranolol, thioridazin and tolbutamide had only limite effect on the extent of binding buspirone to plasma proteins.
Serotonergic agents	CS	↑ Serotonin syndrome/toxicity	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 7 WARNINGS AND PRECAUTIONS, Neurologic, Serotonin Toxicity/Serotonin Syndrome). Seizures have been reported rarely in patients taking this combination.
Trazodone	C	↑SGPT	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.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
Drugs That Inhibit Cytochrome P450 3A4 (CYP3A4)	T	↑ Buspirone	Buspirone has been shown in vitro to be metabolized by CYP3A4. Substances that inhibit CYP3A4, such as ketoconazole or ritonavir, may inhibit buspirone metabolism and increase plasma concentrations of buspirone. 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.
• Cimetidine	CT	↑ Buspirone	Coadministration of buspirone and cimetidine was found to increase Cmax (40%) and Tmax (2-fold) of buspirone, but had minimal effect on AUC of buspirone.
• Diltiazem	CT	↑ Buspirone	In a study of nine healthy volunteers, administration of buspirone (10 mg as a single dose) with diltiazem (60 mg t.i.d.) increased plasma buspirone concentrations. The AUC and Cmax of buspirone were increased 5.3-fold and 4-fold, respectively. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with diltiazem. Subsequent dose adjustments of either drug should be based on clinical response.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
• Erythromycin	CT	↑ Buspirone	The coadministration of buspirone (10 mg as a single dose) and erythromycin (1.5 g/day for 4 days) to healthy volunteers increased plasma buspirone concentrations (5-fold increase in Cmax and a 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of adverse events attributable to buspirone. If buspirone and erythromycin are to be used in combination, a low dose of buspirone (e.g., 2.5 mg b.i.d.) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.
• Itraconazole	CT	↑ Buspirone	The coadministration of buspirone (10 mg as a single dose) and itraconazole (200 mg/day for 4 days) to healthy volunteers increased plasma buspirone concentrations (13-fold increase in Cmax and 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.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
• Nefazodone	CT	↑ Buspirone ↓ 1-pyrimidinylpiperazine	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
• Rifampicin	CT	↓ Buspirone	In a study in healthy volunteers, coadministration of buspirone (30 mg as a single dose) with

			rifampicin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in Cmax and 89.6% decrease in AUC) and pharmacodynamic effects of buspirone.

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
• Verapamil	CT	↑ Buspirone	In a study of nine healthy volunteers, administration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) increased plasma buspirone concentrations. The AUC and Cmax of buspirone were increased 3.4-fold. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with verapamil. Subsequent dose adjustments of either drug should be based on clinical response.
Drugs That induce Cytochrome P450 3A4 (CYP3A4	T	↓ Buspirone	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.

9.5 Drug-Food Interactions

Food may decrease the extent of presystemic clearance of buspirone (see 10.3 Pharmacokinetics, Special Populations and Conditions, Effect on Food).

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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

Buspirone shares some of the properties of the benzodiazepines and the neuroleptics, as well as demonstrating other pharmacological action. Buspirone 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 $5\text{-}HT_{1A}$ 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.

10.2 Pharmacodynamics

Despite sharing some properties with both the benzodiazepines and the neuroleptics, buspirone has a distinct pharmacological profile.

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. (see 16 NON-CLINICAL TOXICOLOGY, Special Toxicology, Abuse Liability, Abuse Liability).

10.3 Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

Buspirone is metabolized primarily by oxidation, which in vitro has been shown to be mediated by Cytochrome P450 3A4 (CYP3A4) (see 9.4 Drug-Drug 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.

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 α2-adrenoceptors (IC50 approximately 25 nM) but virtually inactive at other binding sites.

Elimination

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

Special Populations and Conditions

- **Sex:** No significant differences in buspirone pharmacokinetics as a function of age and/or sex were found.
- **Hepatic/Renal Insufficiency:** Buspirone had no effect on hepatic microsomal enzyme activity when administered to rats for 5 days. In man, the effect of buspirone on drug metabolism or concomitant drug disposition has not been studied. Buspirone clearance is reduced in patients with hepatic impairment as well as in patients with impaired renal function.
- **Effect on Food:** 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.

11 STORAGE, STABILITY AND DISPOSAL

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

Disposal: JAMP Buspirone should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

12 SPECIAL HANDLING INSTRUCTIONS

JAMP Buspirone should be kept in a safe place, such as under lock and out of the sight and reach of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

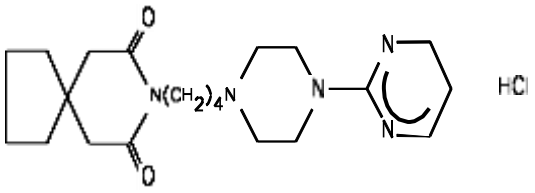
Proper name: Buspirone Hydrochloride

Chemical name: 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.

Molecular formula and molecular mass: $C_{21}H_{31}N_5O_2HCl$ and 421.97 g/mol

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

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.

14.2 Comparative Bioavailability Studies

JAMP 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.).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity:

Species	Sex	Route	LD50 (95% Confidence Interval) mg/Kg
Rat (Adult)	Males	Oral	265 (174-404)
Rat (Adult)	Males/Females	Oral	196 (152-252)
Rat (Newborn)	Males/Females	Oral	415 (332-520)
Mouse	Males	Oral	655 (529-811)
Dog	Males/Females	Oral	586 (371-925)
Monkey	Males/Females	Oral	356 (302-420)
Rat (Adult)	Males/Females	Intraperitoneal	136 (122-152)
Mouse	Males	Intraperitoneal	164 (145-185)
Mouse	Males	Intravenous	73.3 (66.6-80.6)
Monkey	Males/Females	Intravenous	54.3 (47.6-61.9)
Dog	Females	Intravenous infusion	125.3 (lowest lethal dose - infused at 80 mg/Kg/hr - 30.8 mL/hr)

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

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

Subacute Toxicity:

- **Dog:** In a two-week dose ranging study, one male and one female dog per group received

73, 110 or 146 mg/Kg buspirone orally immediately after feeding. Both high dose dogs died on day 5 following convulsions. The mid dose male died on day 11, probably due to acute gastric dilatation. Reddening of gastric mucosa was observed at necropsy in all three dogs that died.

- **Rat:** In a three-month study, groups of 15 males and 15 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.

Reproductive and Developmental Toxicology

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 postpartum. 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.

Special Toxicology

Abuse Liability: 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. **PrAPO-BUSPIRONE** (Buspirone Hydrochloride Tablets USP 10 mg), submission control No. 259719, Product Monograph, APOTEX INC., Date of Revision: Jun 03, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrJAMP Buspirone

Buspirone Hydrochloride Tablets USP

Read this carefully before you start taking **JAMP Buspirone** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JAMP Buspirone**.

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take JAMP Buspirone exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take JAMP Buspirone with:

- opioids
- alcohol or
- illicit drugs

Your doctor should:

- talk to you about the risks of treatment with JAMP Buspirone as well as other treatment (including non-drug) options
- assess your risk for these behaviours before prescribing JAMP Buspirone
- monitor you while you are taking JAMP Buspirone for the signs and symptoms of misuse and abuse. If you feel like you are craving JAMP Buspirone, or not using it as directed, talk to your doctor right away.

Store JAMP Buspirone in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking JAMP Buspirone, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Other warnings you should know about)

- Always contact your doctor before stopping, or lowering your dose of JAMP Buspirone or changing your medicine.

JAMP Buspirone with Opioids: Taking JAMP Buspirone with opioid medicines can cause:

- severe drowsiness
- decreased awareness
- breathing problems
- coma
- death

What is JAMP Buspirone used for?

JAMP Buspirone is used for the short-term relief of anxiety symptoms in adults with Generalized Anxiety Disorder. Do not use JAMP Buspirone long term.
If you are 65 years or older, talk to your doctor before starting JAMP Buspirone. JAMP Buspirone may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

How does JAMP Buspirone work?

JAMP Buspirone belongs to a group of medicines called anxiolytics. These medicines change the levels of chemicals in the brain, which can help make you feel less anxious.

What are the ingredients in JAMP Buspirone?

Medicinal ingredients: Buspirone hydrochloride

Non-medicinal ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

JAMP Buspirone comes in the following dosage forms:

Tablets 10 mg

Do not use JAMP Buspirone if:

- you are allergic to buspirone hydrochloride or any ingredient in JAMP Buspirone
- you have severe liver or kidney problems
- you are taking, or have taken within the past 14 days, a monoamine oxidase (MAO) inhibitor medication (such as methylene blue and linezolid)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take JAMP Buspirone. Talk about any health conditions or problems you may have, including if you:

- have taken benzodiazepines
- have or had liver or kidney problems
- are pregnant or trying to become pregnant
- are breastfeeding
- are 65 years of age or older
- are allergic to lactose
- have ever had a problem with:
    - substance use, including prescribed or illegal drugs, or
    - alcohol
- have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)

Other warnings you should know about:

Extrapyramidal symptoms: JAMP Buspirone may cause extrapyramidal symptoms. Symptoms include tremors, slurred speech, muscle spasm of the neck, shoulders or body, restlessness, and rigid muscles.

Serotonin toxicity (also know as Serotonin syndrome): JAMP Buspirone can cause serotonin toxicity, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles
and digestive system work. You may develop serotonin toxicity if you take JAMP Buspirone with certain anti-depressants or migraine medications.

Serotonin toxicity symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Driving and using machines: JAMP Buspirone may make you feel dizzy. Do not drive or do tasks that need special attention until you know how you respond to JAMP Buspirone.

Withdrawal: If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop JAMP Buspirone.

Your risk of going through withdrawal is higher if you are taking JAMP Buspirone for a long time or at high doses. However, symptoms can still occur if you are taking JAMP Buspirone as directed for a short period of time or slowly reducing the dose.

The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).

Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.

Severe symptoms of withdrawal include:

- feeling like you cannot move or respond (catatonia)
- severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
- feeling depressed
- feeling disconnected from reality (dissociation)
- seeing or hearing things that are not there (hallucinations)
- overactive behavior and thoughts (mania)
- believing in things that are not true (psychosis)
- convulsions (seizures), including some that do not stop
- thoughts or actions of suicide

For other symptoms of withdrawal, see the **Serious side effects and what to do about them** table (below).

To reduce your chances of going through withdrawal:

- always contact your doctor before stopping or reducing your dose of JAMP Buspirone or changing medications
- always follow your doctor's instructions on how to reduce your dose carefully and safely
- tell your doctor right away if you experience any unusual symptoms after changing or stopping your treatment

JAMP Buspirone with Opioids: Taking JAMP Buspirone with opioid medicines can cause severe drowsiness and breathing problems.

Tell your doctor if you:

- are taking opioid medicines
- are prescribed an opioid medicine after you start taking JAMP Buspirone

Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and JAMP Buspirone affects you.

Falls and Fractures: Benzodiazepines like JAMP Buspirone can cause you to feel sleepy, dizzy and affect your balance. This increases your risks of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JAMP Buspirone:

Serious Drug Interactions

Taking JAMP Buspirone and opioids may cause:

- severe drowsiness
- trouble breathing
- coma
- death

- Food
- Medicines used to treat depression such as serotonergic agents, monoamine

oxidase inhibitors and trazodone
- Medicines used to treat mental health problems such as haloperidol, diazepam, and nefazodone
- Medicines used to treat high blood pressure such as propranolol, diltiazem and verapamil
- Medicine used to prevent blood clots called warfarin
- Medicine used to treat heart failure called digoxin
- Medicines used to treat infections such as erythromycin, rifampicin, ketoconazole and itraconazole
- Medicine used to treat HIV called ritonavir
- Medicine used to treat inflammation called dexamethasone
- Medicines used to treat epilepsy such as phenytoin, phenobarbital, and carbamazepine
- Medicine used to treat ulcers called cimetidine
- Grapefruit or grapefruit juice
- Alcohol. Do not drink alcohol while taking this medication.

How to take JAMP Buspirone:

- Take JAMP Buspirone exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.

Usual dose:

- The starting adult dose is 5 mg two to three times a day.
- Based on your response and tolerability, your healthcare professional may increase your dose.
- The usual adult dose is 20 mg to 30 mg in two to three divided doses. If you have liver or kidney problems, your doctor may prescribe you a lower dose.
- The maximum daily adult dose is 45 mg. Do not increase the prescribed dose of JAMP Buspirone unless told to by your healthcare professional.
- Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

Overdose:

Signs of an overdose include:

- drowsiness,
- difficulty balancing and speaking,
- nausea and vomiting,
- dizziness,
- clammy feeling,
- trouble thinking,
- feeling pleasure or excitement,
- upset stomach or indigestion,
- headache,
- itching,
- narrowing eye pupil,

- low blood pressure,
- tremor,
- incoordination,
- difficulty sleeping (insomnia) and
- seeing or believing things that are not there (hallucinations).

If you think you, or a person you are caring for, have taken too much JAMP Buspirone, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have forgotten to take your dose, carry on and take your next dose at the usual time. Do not try to make up for a missed dose by taking a double dose the next time.

What are possible side effects from using JAMP Buspirone?
These are not all the possible side effects you may have when taking JAMP Buspirone. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Falls and fractures
- Sweating and clamminess
- Dry mouth
- Constipation
- Diarrhea
- Being sick (vomiting)
- Dizziness
- Headache
- Nervousness
- Light-headedness
- Nausea
- Muscle aches, pain, cramps or spasms
- Frequent urination at night (nocturia) or bed-wetting (enuresis)
- Ringing, buzzing clicking or hissing in the ears (tinnitus)
- Rash or itchiness
- Eye problems such as sore eyes, pressure on eyes, blurred vision, red or itchy eyes
- Irregular menstruation, missing one or more menstrual period
- Decreased or increased sexual desire
- Delayed ejaculation or impotence
- Stiff neck or jaw

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Chest pain		√	
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		√	
COMMON			
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		√	
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing.		√	
Rectal bleeding: black, tarry stool, blood in the stool		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		√	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish color to your lips and skin, racing pulse or heart palpitations		√	
Arthralgia: joint pain		√	
Skin problems: Easy bruising, a painful skin condition where fluid fills a space between layers of skin (blisters)		√	
RARE			
Congestive Heart Failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Myocardial infarction (heart attack): pressure or squeezing pain between the shoulder blades, in the chest, jaw, left arm or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat.			**√**
Cardiomyopathy (signs of heart muscle disease): breathlessness or swelling of the legs			**√**
Bradycardia (abnormally slow heartbeat)			**√**
Thyroid gland problems: body aches, fatigue, low blood pressure, light-headedness, loss of body hair, skin discoloration, unexplained weight loss		**√**	
Stroke: Sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body; sudden confusion, difficulty speaking or understanding others; sudden difficulty in walking or loss of balance or coordination; suddenly feeling dizzy or sudden severe headache with no known cause.			**√**
Serotonin toxicity: a reaction which may cause feelings of agitation or restlessness, flushing, muscle twitching, involuntary eye movements, heavy sweating, high body temperature (>38 °C), or rigid muscles.		**√**	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat		**√**	
Leukopenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		**√**	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		**√**	
UNKNOWN			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Overdose: extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.		√	
Respiratory Depression: slow, shallow or weak breathing.			√
Withdrawal: **Severe symptoms include:** **Catatonia:** feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms, legs or feet; sweating.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°-30°C) in tight, light-resistant containers. Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

Keep out of reach and sight of children.

If you want more information about JAMP Buspirone:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.jamppharma.com) or by calling at 1 866-399-9091.

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Last Revised: February 10, 2023