1. Product Name

PACIFIC BUSPIRONE, 5 mg and 10 mg, tablet.

2. Qualitative and Quantitative Composition

Each tablet contains 5 mg or 10 mg of buspirone hydrochloride.

PACIFIC BUSPIRONE tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

5 mg tablets: white, round tablet with "BR 5" embossed on one side and "G" on the other.

10 mg tablets: white, capsule shaped tablet embossed “BR (breakline) 10” on one side and “G” on the other.

4. Clinical Particulars

4.1 Therapeutic 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.

4.2 Dose and method of administration

The usual starting dose is 5 mg given 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 depending upon the therapeutic response to a maximum daily dose of 60 mg. After dosage titration the usual daily dose will be 20 to 30 mg 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 section 5.2).

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 section 4.5).

Grapefruit juice increases the plasma concentrations of buspirone. Patients taking buspirone should avoid consuming grapefruit juice (see section 4.5).

Special populations
Renal or hepatic impairment
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 section 4.4).

4.3 Contraindications

Hypersensitivity to buspirone hydrochloride or any of the inactive ingredients listed in section 6.1.

Severe (biopsy proven cirrhosis) hepatic impairment.

4.4 Special warnings and precautions for use

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 disorders
The effects of buspirone have not been evaluated in patients with a history of convulsive disorders. Buspirone lacks anticonvulsant activities in animals. Therefore, 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 or may be contraindicated (see section 4.3). Buspirone clearance is reduced in patients with hepatic cirrhosis. In one study, a single 20 mg 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.
Central dopaminergic receptor binding
The possibility of acute and chronic changes in dopamine mediated neurological function (e.g. dystonia, pseudo-Parkinsonism, akathisia and tardive dyskinesia) should be considered since animal studies have shown that buspirone can bind to central dopamine receptors.

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.

Previous benzodiazepine treatment and potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients
Patients who have previously taken benzodiazepines may be less likely to respond to buspirone than those who have not. In 2 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. There is also no evidence that buspirone will block the withdrawal symptoms often seen with cessation of therapy with sedative or hypnotic therapy in drug dependent patients.

Therefore, if it is considered desirable to switch a patient from benzodiazepine or sedative/hypnotic therapy to buspirone, the benzodiazepine or sedative/hypnotic should first be withdrawn gradually. A drug free interval is desirable between withdrawal of the previous therapy and initiation of buspirone, in order to increase the likelihood of distinguishing between withdrawal effects and unrelieved anxiety.

Paediatric use
The safety and effectiveness of buspirone in individuals below the age of 18 years has not been established.

Drug abuse and dependence
Buspirone has shown no potential for drug abuse and dependence based on limited human and animal studies. In double-blind clinical studies using human volunteers with a history of recreational drug or alcohol usage, none of the subjects was able to distinguish between buspirone and placebo. By contrast, subjects showed a statistically significant preference for methaqualone and diazepam. Short term studies in monkeys, mice and rats have shown that buspirone lacks potential for abuse.

Patients with a history of drug abuse should be carefully evaluated and followed closely for signs of buspirone abuse and misuse.

No withdrawal reactions have been reported on cessation of buspirone therapy. Following chronic administration in the rat, abrupt withdrawal of buspirone did not result in the loss of body weight commonly observed with substances that cause physical dependence.

Use in the elderly
Buspirone has not been systematically evaluated in older patients. No unusual age-related phenomena have been identified in the several hundred elderly patients who have participated in clinical trials. 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.

4.5 Interaction with other medicines and other forms of interaction
Alcohol
Buspirone does not significantly augment the depressant effects of alcohol. The functional capabilities of buspirone treated subjects who ingested alcohol were not significantly different from those who ingested alcohol plus placebo. In combination with alcohol, buspirone showed significantly less impairment of psychomotor and information processing functions than did either diazepam or lorazepam. However, it is prudent to avoid concomitant use with alcohol.

**Food**

Food increases the bioavailability of unchanged buspirone in healthy subjects, possibly due to a reduced first-pass effect (see section 5.2).

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, co-administration of buspirone (10 mg as a single dose) with double-strength grapefruit juice (200 mL double-strength three times daily for 2 days) increased plasma buspirone concentrations (4.3-fold increase in $C_{\text{max}}$ and 9.2-fold increase in AUC (see section 4.5).

**CNS-active drugs**

The concomitant use of buspirone with other CNS-active drugs should be approached with caution (see section 4.4).

**Monoamine oxidase inhibitors**

Spontaneous voluntary reports have described the occurrence of elevated blood pressure in patients receiving both buspirone and monoamine oxidase inhibitors (phenelzine sulfate or tranylcypromine sulfate). Therefore, it is recommended that buspirone not be used concomitantly with a monoamine oxidase inhibitor (MAOI).

**Selective serotonin re-uptake inhibitors**

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.

**Diazepam**

After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters have been observed, but significantly higher levels of the metabolite nordiazepam were seen, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

**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.

**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, and 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 section 4.2) used cautiously, is recommended. Subsequent dose adjustments of either drug should be based on clinical response.
Nefazodone
The co-administration 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 co-administered with nefazodone. Subsequent dose adjustments of either drug should be based on clinical response.

Cimetidine
Co-administration of buspirone and cimetidine was found to increase $C_{\text{max}}$ (40%) and $T_{\text{max}}$ (2-fold), but had minimal effect on AUC of buspirone.

Erythromycin
The co-administration 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 $C_{\text{max}}$ and a 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of adverse events attributable to buspirone. If buspirone and erythromycin are to be used in combination, a low dose of buspirone (e.g. 2.5 mg twice a day) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Itraconazole
The co-administration 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 $C_{\text{max}}$ 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 (10 mg as a single dose) with diltiazem (60 mg three times a day) increased plasma buspirone concentrations. The AUC and $C_{\text{max}}$ 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 (10 mg as a single dose) with verapamil (80 mg three times a day) increased plasma buspirone concentrations. The AUC and $C_{\text{max}}$ 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, co-administration of buspirone (10 mg as a single dose) with rifampicin (600 mg/day for 5 days) decreased the plasma concentrations (83.7% decrease in $C_{\text{max}}$ 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.

Other Drugs

No alterations in the pharmacokinetics of amitriptyline have been observed during concomitant administration with buspirone.

The possibility of interaction with other drugs acting on dopamine receptors has not been excluded.

In vitro 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.

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.

Drug/Laboratory test interactions

Buspirone does not appear to interfere with commonly employed clinical laboratory tests. Stimulation of prolactin and growth hormone have been observed after single oral doses of 100 mg buspirone. However, chronic (28 day) administration at recommended therapeutic doses has no effect on plasma cortisol, growth hormone or prolactin levels.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B1.

Fertility impairment or foetal damage was not observed in reproduction studies performed in rats and rabbits at doses of buspirone up to 36 mg/kg orally. In humans, however, adequate and well controlled studies during pregnancy have not been performed. 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 on labour and delivery in women is unknown.

Breast-feeding

The extent of excretion in human milk of buspirone or its metabolites is not known. In rats, however, 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 outweighs the potential risk to the breastfed infant.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

The most common adverse reactions encountered with buspirone are dizziness, headache, drowsiness and nausea.

Treatment withdrawals

Approximately 10% of the 2200 patients who participated in buspirone pre-marketing clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation included: central nervous system disturbance (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.

Placebo-controlled Studies

Incidence rates of adverse events reported by patients from 17 double-blind placebo-controlled studies with buspirone (n=477) showed that only for dizziness (12%), nausea (8%), nervousness (5%), headache (6%), light-headedness (3%), excitement (2%) and sweating/clamminess were the incidences observed with buspirone significantly (p ≤ 0.05) higher than with placebo.

Other events observed pre- and post-marketing

During its pre-marketing assessment, buspirone was evaluated in over 2700 subjects. 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 with certainty.

The following enumeration by organ system describes events in terms of their relative frequency of reporting. Events of major clinical importance are also described in the Warnings and Precautions section.

The following definitions of frequency are used:

Common (in at least 1/100 patients); uncommon (in 1/100 to 1/1000 patients); rare (in less than 1/1000 patients).

Cardiovascular

Common: non-specific chest pain, tachycardia/palpitations;
Uncommon: syncope, hypotension, hypertension;
Rare: cerebrovascular accident, myocardial infarction, cardiomyopathy, congestive heart failure, bradycardia.

Central nervous system

Common: drowsiness, insomnia, decreased concentration, depression, confusion, anger/hostility, dream disturbances;
Uncommon: depersonalisation, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction;
Rare: dysphoria, hallucinations, feelings of claustrophobia, cold intolerance, stupor, seizures, slurred speech, extrapyramidal symptoms including dyskinesias (acute & delayed), dystonic reactions, cogwheel rigidity, emotional lability, psychosis, suicidal ideation, ataxias, transient difficulty with recall, serotonin syndrome, dizziness, Parkinsonism, restless leg syndrome, restlessness.

EENT

Common: blurred vision, sore throat, nasal congestion;
Uncommon: tinnitus, redness and itching of the eyes, altered taste, conjunctivitis; Rare: eye pain, altered sense of smell, photophobia, pressure on eyes, inner ear abnormality, tunnel vision.

**Endocrine**
Rare: galactorrhoea.

**Gastrointestinal**
Common: dry mouth, abdominal/gastric distress, diarrhoea, constipation, vomiting; Uncommon: flatulence, anorexia, increased appetite, salivation, rectal bleeding; Rare: irritable colon, burning of the tongue.

**Genitourinary**
Uncommon: urinary frequency, urinary hesitancy, menstrual irregularity or spotting, dysuria; Rare: amenorrhoea, enuresis, nocturia, pelvic inflammatory disease, urinary retention.

**Musculoskeletal**
Common: musculoskeletal aches/pains; Uncommon: muscle cramps, muscle spasms, rigid/stiff muscles; Rare: arthralgias.

**Neurological**
Common: paraesthesia/ numbness, incoordination/tremor; Uncommon: involuntary movements; Rare: paresis, decreased reaction time.

**Respiratory**
Uncommon: shortness of breath, chest congestion; Rare: hyperventilation, epistaxis.

**Sexual function**
Uncommon: decreased or increased libido; Rare: delayed ejaculation, impotence.

**Skin**
Common: rash; Uncommon: oedema, pruritus, flushing, easy bruising, dry skin, facial oedema; Rare: acne, hair loss, blisters, thinning of nails.

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

**Clinical laboratory**
Uncommon: mild increases in hepatic aminotransferases (AST, ALT); Rare: eosinophilia, leucopenia, thrombocytopaenia.

**Miscellaneous**
Common: fatigue/ weakness, sweating/clamminess; Uncommon: weight gain, fever, roaring sensation in the head, weight loss, malaise; Rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs, thyroid abnormality.
Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions [https://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/).

4.9 Overdose

Signs and symptoms

In healthy normal human subjects, the maximum tolerated dose of buspirone is 375 mg per day. As the maximum dose levels were reached, the following symptoms were most commonly observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans with deliberate or accidental overdosage of buspirone alone.

Treatment

General symptomatic and supportive measures should be used along with activated charcoal. Respiration, pulse and blood pressure should be monitored in all cases of overdosage. No specific antidote is known for buspirone. Dialysis does not modify the blood levels of buspirone in anuric patients. The buspirone metabolite 1-PP is partially removed by haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, ATC code: N05BE01

Buspirone hydrochloride belongs chemically to the class of pharmacologic agents with selective anxiolytic psychotropic activity known as the azapirones.

Mechanism of action

The mechanism of action of buspirone is unknown. In contrast to the benzodiazepines, and other anxiolytic agents, buspirone does not exert anticonvulsant or muscle relaxant effects. It also lacks the prominent sedative effect that is associated with more typical anxiolytics. In vitro preclinical studies have shown that buspirone has a high affinity for serotonin (5-HT1A) receptors. Buspirone has no significant affinity for benzodiazepine receptors and does not affect GABA binding in vitro or in vivo when tested in preclinical models.

Buspirone has moderate affinity for brain D2-dopamine receptors. Some studies do suggest that buspirone may have indirect effects on other neurotransmitter systems.

Clinical efficacy and safety

In controlled clinical trials, patients who received buspirone did not differ significantly from those who received placebo with respect to sedation (drowsiness and/or fatigue) or with respect to functional impairment. In contrast, both diazepam and clorazepate produced significant sedation, and diazepam and lorazepam produced significant functional impairment. As part of the clinical trial programme 46 healthy subjects received buspirone 10 or 20 mg (15 also received alcohol) and undertook a driving simulator test (to measure motor vehicle driving skills) and showed little to no functional impairment due to buspirone.

5.2 Pharmacokinetic properties

Absorption
Buspirone is rapidly absorbed in man and undergoes extensive first pass metabolism. Peak plasma levels are attained 60 to 90 minutes after ingestion. However, in some normal individuals C\(_{\text{max}}\) may occur after several hours. Hepatic cirrhosis can delay C\(_{\text{max}}\) markedly; with an average of 19.3 hours (range 1.1-51.3h) while renal impairment produces a less marked prolongation of about 6-7 hours (range 0.5-15.5h).

At doses of 10, 20 and 40 mg, the mean peak plasma concentrations attained were respectively, 0.9, 1.7 and 3.2 nanograms/mL. These data suggest a proportional relationship exists between plasma concentration and dosage. Multiple dose studies for up to 28 days in subjects with normal renal and hepatic function indicate that steady state plasma concentrations are achieved within 2 days and that plasma concentration is proportional to dose. Once steady state is achieved, the plasma concentration of buspirone is not markedly altered by chronic administration. At a given dose, considerable intersubject variation in buspirone levels can occur.

**Distribution**

In man, approximately 95% of buspirone is protein bound, but other highly bind drugs, e.g. phenytoin, propranolol and warfarin, are not displaced by buspirone from plasma proteins *in vitro*.

**Metabolism**

Buspirone undergoes extensive first pass metabolism.

Buspirone is metabolised primarily by oxidation producing several hydroxylated derivatives and a pharmacologically active metabolite, 1-pyrimidinylpiperazine (1-PP). In animal models that are predictive of anxiolytic potential in man, 1-PP has about one quarter or less of the activity of buspirone.

**Excretion**

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 ranged from 2±1 to 11±3 hours. Women tended to have slightly but not statistically significantly longer half-life values than men. After a single dose of buspirone, 29 to 63% of the dose was excreted in the urine within 24 hours primarily as metabolites; faecal excretion accounted for 18 to 38% of the dose.

**In renal or hepatic impairment**

Buspirone clearance is reduced in patients with hepatic impairment as well as in patients with impaired renal function (see sections 4.3 and 4.4).

**Effect of food**

The effect of food on the bioavailability of buspirone was studied in 8 subjects. The area under the plasma concentration curve (AUC) and peak plasma concentration (C\(_{\text{max}}\)) of unchanged buspirone increased by 84% and 116% respectively when the drug was administered with food, but the total amount of buspirone immunoreactive material did not change. This suggests that food may decrease the extent of presystemic clearance of buspirone, but the clinical significance of these findings is unknown (see section 4.2).

**5.3 Preclinical safety data**

**Animal toxicology**

Toxicology studies of buspirone indicate the following LD 50 values: 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.

**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 \textit{in vitro} when tested using Salmonella typhimurium (Ames Test) or mouse lymphoma L5178YTK+ cell cultures. DNA damage was not observed with buspirone using \textit{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.

### 6. Pharmaceutical Particulars

#### 6.1 List of excipients

Each Pacific Buspirone tablet also contains lactose monohydrate, microcrystalline cellulose, sodium starch glycollate, colloidal silicon dioxide and magnesium stearate.

PACIFIC BUSPIRONE are gluten free.

#### 6.2 Incompatibilities

Not applicable.

#### 6.3 Shelf life

3 years.

#### 6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

#### 6.5 Nature and contents of container

HDPE bottle with PP lid. Pack size of 100 tablets

Al/PVC blister packs of 30 tablets

Al/PVC/PVdC blister packs of 30 tablets

Not all pack types and sizes may be marketed.

#### 6.6 Special precautions for disposal

Not applicable.

### 7. Medicines Schedule

Prescription Medicine

### 8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792
9. Date of First Approval

4 July 2002

10. Date of Revision of the Text

27 June 2018 Revised to SmPC format