AUSTRALIAN PRODUCT INFORMATION – ANKSILON™ (buspirone hydrochloride) tablets

1. NAME OF THE MEDICINE

Buspirone hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ANKSILON tablets contain either 5 mg or 10 mg of buspirone hydrochloride.

Excipients with known effect: sugars as lactose.

For the full list of excipients, see Section **6.1 List of excipients**.

3. PHARMACEUTICAL FORM

5 mg tablets: white or almost white, oval biconvex tablets debossed with 'ORN 30' on one side and a score on the other side.

10 mg tablets: white or almost white, oval biconvex tablets debossed with 'ORN 31' on one side and a score on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ANKSILON (buspirone hydrochloride) is indicated for the short-term treatment of anxiety.

The ordinary anxiety and tension associated with the stress of everyday life usually does not require treatment with an anxiolytic agent.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

The recommended initial dose is 15 mg daily (5 mg three times a day).

To achieve an optimal therapeutic response, each 2 to 3 days the dosage may be increased 5 mg per day as needed. The maximum daily dosage should not exceed 60 mg per day. In most patients, an optimal therapeutic response is obtained by titration to a total daily dose of 20-30 mg given in 2 to 3 divided doses.

Food increases the bioavailability of buspirone. ANKSILON should be taken at the same time each day and consistently with or without food (see Section **5.2 Pharmacokinetic properties: Effect of food**).

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 Interactions with other medicines and other forms of interactions**).

Grapefruit juice increases the plasma concentrations of buspirone. Patients taking ANKSILON should avoid consuming grapefruit juice (see Section **4.5 Interactions with other medicines and other forms of interactions**).

Use in the elderly

In one study, no significant difference in buspirone pharmacokinetics was found between elderly patients and healthy volunteers. The maximum daily dose in the elderly should not exceed 30 mg/day (see Section **4.4 Special warnings and precautions for use**).

Dosage adjustment in renal or hepatic impairment

See Section **4.4 Special warnings and precautions for use**.

Instructions for changing patients from benzodiazepine therapy to ANKSILON

To switch a patient from benzodiazepine therapy to ANKSILON, it is important to discontinue the benzodiazepine therapy by gradually decreasing the dose as recommended in the benzodiazepine product information, particularly in patients who have been on prolonged and/or high-dose therapy and may be physically-dependent on benzodiazepines.

Benzodiazepine rebound or withdrawal symptoms may occur over varying time periods, depending in part on the half-life of the drug and rate of elimination. These symptoms, such as irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, and convulsions, should be treated symptomatically. ANKSILON will not control benzodiazepine withdrawal symptoms.

When the physician is confident that the patient has been properly withdrawn from benzodiazepine therapy, ANKSILON should be initiated at a dosage of 5 mg three times daily, and if necessary, titrated in 5 mg increments every two to three days until optimal therapeutic effect is obtained.

4.3 CONTRAINDICATIONS

ANKSILON should not be administered to patients with:

- Hypersensitivity to buspirone hydrochloride or other ingredients listed in Section **6.1 List of excipients**.
- Severe hepatic impairment (biopsy proven cirrhosis).
- Severe renal insufficiency (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2)
- Acute angle-closure glaucoma
- *Myasthenia gravis*
- Epilepsy
- Acute intoxication with alcohol, hypnotics, analgesics or antipsychotic drugs

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Monoamine oxidase inhibitors (MAOIs)

The administration of ANKSILON 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 hydrochloride has been added to a regimen including a MAOI. Therefore it is recommended that ANKSILON should not be used concomitantly with a 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, ANKSILON is not recommended for patients with a history of seizure disorders.

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

Because buspirone can bind to central serotonin and dopamine receptors as well as increase noradrenergic activity, and its mechanism of action is not fully elucidated, long-term toxicity in the CNS or other organ systems cannot be predicted.

If long-term medical treatment is necessary, it should be monitored intensively. The need to continue treatment should be periodically reassessed, and discontinuation of treatment after a longer period of time (several months) should be considered.

Psycho- and sociotherapeutic measures should not be neglected during treatment with buspirone.

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 ANKSILON, 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 ANKSILON, in order to increase the likelihood of distinguishing between withdrawal effects and unrelieved anxiety.(see Section **4.2 Dose and method of administration: Instructions for changing patients from benzodiazepine therapy to ANKSILON**)

Drug addiction and dependence

Buspirone has shown no potential for drug addiction and dependence based on limited human and animal studies. Human volunteers with a history of recreational drug or alcohol usage were used in two double-blind clinical studies. None of the subjects was able to distinguish between buspirone hydrochloride 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 hydrochloride lacks potential for abuse.

Patients with a history of substance use disorder should be carefully evaluated and followed closely for signs of buspirone addiction or non-prescribed use.

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

Use in hepatic impairment

ANKSILON should be used cautiously, at reduced doses, in patients with impaired hepatic function or may be contraindicated (see Section **4.3 Contraindications**). 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 AUC respectively in cirrhotic patients compared to normal volunteers. Administration of ANKSILON to patients with severe hepatic impairment is contraindicated.

Use in renal impairment

ANKSILON 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 ANKSILON should not be administered to patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73m^2) (see Section **4.3 Contraindications**).

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 ANKSILON should be used in the elderly at doses not exceeding 30 mg/day.

Paediatric use

ANKSILON should not be given to children and adolescents under 18 years of age since the safety and effectiveness of buspirone in this age group have not been established.

Effects on laboratory tests

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 hydrochloride. However, chronic (28 day) administration at recommended therapeutic doses has no effect on plasma cortisol, growth hormone or prolactin levels.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 **4.2 Dose and method of administration**).

Grapefruit or grapefruit juice

As grapefruit juice is an inhibitor of CYP3A4, eating grapefruit or drinking the juice should be avoided during treatment with ANKSILON. In a study in healthy volunteers, coadministration of buspirone hydrochloride (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.

CNS-active drugs

The concomitant use of ANKSILON with other CNS-active drugs should be approached with caution.

Monoamine oxidase inhibitors (MAOIs)

See Section **4.4 Special warnings and precautions for use**.

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 ANKSILON not be used concomitantly with a monoamine oxidase inhibitor.

Selective serotonin re-uptake inhibitors

Seizures have been reported rarely in patients taking buspirone and SSRIs.

Buspirone should be used with caution in combination with serotonergic drugs (including MAOIs, tryptophan, triptans, tramadol, buprenorphine, linezolid, SSRIs, lithium and St John's wort) as there are isolated reports of serotonin syndrome occurring in patients on concomitant SSRI therapy. If this condition is suspected, treatment with buspirone should be immediately discontinued and supportive symptomatic treatment should be initiated.

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 pharmacokinetics of diazepam have been observed but significantly higher levels of the metabolite nordiazepam were seen and minor clinical effects (dizziness, headache, and nausea) were observed.

Fluvoxamine

In one study of ten healthy volunteers who received 5 days of treatment with fluvoxamine 100 mg daily followed by a single dose of buspirone 10 mg, the plasma buspirone $AUC_{0-\infty}$ was increased 2.4 fold ($P < 0.05$) and C_{max} 2.0 fold ($P < 0.05$) by fluvoxamine, compared with placebo.

Trazodone

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.

Drugs that inhibit Cytochrome P_{450} $IIIA_4$ (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 ANKSILON is to be used in combination with a potent inhibitor of CYP3A4, a low dose of buspirone (see below for specific dosage recommendations), used cautiously, is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Nefazodone

The co-administration 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 (17%) and mCPP (9%). Slight increases in C_{max} were observed for nefazodone (9%) and its metabolite HO-NEF (11%).

The side effect profile for subjects receiving buspirone 2.5 mg 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 light-headedness, 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_{max} (40%) and T_{max} (2-fold), but had minimal effect on the AUC of buspirone. Because of the high protein binding of buspirone (around 95%), caution is advised when drugs with high protein binding are given concomitantly.

Baclofen, lofexidine, nabilone, antihistamines may enhance any sedative effect.

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_{max} and a 6-fold increase in AUC). These pharmacokinetic interactions were accompanied by an increased incidence of adverse events attributable to buspirone. If buspirone and erythromycin are to be used in combination, a low dose of buspirone (e.g. 2.5 mg b.i.d.) is recommended. Subsequent dose adjustments of either medicine 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_{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 t.i.d.) increased plasma buspirone concentrations. The AUC and C_{max} of buspirone were increased 5.5-fold and 4-fold, respectively. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with diltiazem. Subsequent dose adjustments of either drug should be based on clinical response.

Verapamil

In a study of nine healthy volunteers, administration of buspirone (10 mg as a single dose) with verapamil (80 mg t.i.d.) increased plasma buspirone concentrations. The AUC and C_{max} of buspirone were increased 3.4-fold. Enhanced effects and increased toxicity of buspirone may be possible when buspirone is administered with verapamil. Subsequent dose adjustments of either drug should be based on clinical response.

Rifampicin

In a study of 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_{max} and 89.6% decrease in AUC) and pharmacodynamic effects of buspirone.

Other inducers of CYP3A4

Substances that induce CYP3A4, such as dexamethasone, St John's Wort (*Hypericum perforatum*), 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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.

Use in pregnancy

Category B1 [1]

In humans, however, adequate and well controlled studies during pregnancy have **not** been performed. Therefore, use of ANKSILON 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.

Use in lactation

The extent of the excretion in human milk of buspirone or its metabolites is not known. In rats, however, buspirone and its metabolites are excreted in milk. Therefore, ANKSILON should be administered to breast feeding women only after the attending physician has determined that the benefit to the mother outweighs the potential risk to the breast fed infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Studies indicate that buspirone is less sedating than other anxiolytics in that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be advised not to drive or operate machinery until their individual susceptibilities to ANKSILON are known.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Treatment withdrawals

Approximately 10% of the 2200 patients who participated in buspirone premarketing 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,

[1] Category B1: Drugs which have been taken only by a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects in the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

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 ($p \leq 0.05$) higher than with placebo.

Other events observed during premarketing evaluation or post-introduction

During its premarketing 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. As part of the total experience gained in clinical studies, various adverse events were reported. In the absence of appropriate controls in some of the studies a causal relationship to buspirone treatment cannot be determined with certainty.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the database. Events of major clinical importance are also described in Section **4.4 Special warnings and precautions for use**. The following terms of frequency are used:

Common adverse events: defined as those occurring in ≥ 1/100 but < 1/10 patients (≥ 1%; < 10%), *uncommon* adverse events were those occurring in ≥ 1/1000 but < 1/100 patients (≥ 0.1%; < 1%), while *rare* events are those occurring in ≥ 1/10000 and < 1/1000 patients (≥ 0.01%; < 0.1%).

Blood and lymphatic system disorders:

Rare: blood count disorders (eosinophilia, leukopenia, thrombocytopenia), bleeding disorders.

Immune system disorders:

Rare: allergic reactions (including urticaria, ecchymosis, angioedema).

Endocrine system disorders:

Rare: thyroid dysfunction.

Metabolism and nutrition disorders:

Uncommon: increased appetite, anorexia, weight gain, weight loss.

Psychiatric disorders:

Common: dream disturbances, insomnia, nervousness, agitation, anger, hostility, confusion, depression;

Uncommon: depersonalisation, euphoria, dysphoria, akathisia, loss of interest, association disturbances, hallucinations, suicidal ideation, fearfulness;

Rare: emotional lability, claustrophobia, psychosis, alcohol abuse.

Nervous system disorders:

Common: headache, drowsiness, dizziness, light-headedness, impaired concentration, numbness, paraesthesia, loss of coordination, tremors;

Uncommon: involuntary movements, seizures, roaring sensation in the head, altered taste, salivation;

Rare: extrapyramidal symptoms including early and late dyskinesia, dystonic reactions (including dystonia), cogwheel rigidity, parkinsonism, restless legs syndrome, restlessness, decreased reaction time, ataxias, stupor, slurred speech, transient memory gaps, serotonin syndrome, loss of voice.

Eye disorders:

Common: blurred vision;
Uncommon: redness of the eyes, itchy eyes, conjunctivitis;
Rare: eye pain, photophobia, sensation of pressure on the eyes, tunnel vision.

Ear and labyrinth disorders:

Common: tinnitus;
Uncommon: hyperacusis.

Cardiac disorders:

Common: non-specific chest pain, tachycardia/palpitations;
Rare: heart failure, myocardial infarction, cardiomyopathy, bradycardia.

Vascular system disorders:

Uncommon: syncope, hypotension, hypertension;
Rare: cerebrovascular accident.

Respiratory system, thoracic and mediastinal disorders:

Common: sore throat, nasal congestion;
Uncommon: hyperventilation, shortness of breath, chest congestion, altered sense of smell;
Rare: epistaxis.

Gastrointestinal system disorders:

Common: nausea, dry mouth, abdominal/gastric distress, diarrhoea, constipation, vomiting;
Uncommon: rectal bleeding, flatulence, irritable colon;
Rare: burning tongue, hiccups.

Hepatobiliary system disorders:

Uncommon: increased liver enzymes.

Skin and subcutaneous tissue disorders:

Common: rash;
Uncommon: flushing, tendency to bruising, hair loss, dry skin, pruritus, blisters;
Rare: purpura, acne, thinning of nails.

Musculoskeletal system and connective tissue disorders:

Common: musculoskeletal aches/pains;
Uncommon: muscle cramps, muscle tension, muscle spasms, arthralgias;
Rare: paresis.

Renal and urinary system disorders:

Uncommon: urinary frequency, urinary hesitancy, urinary retention, dysuria;
Rare: enuresis, nocturia.

Reproductive system and breast disorders:

Uncommon: menstrual disorders, decreased or increased libido;
Rare: amenorrhea, pelvic inflammatory disease, abnormal ejaculation, impotence, galactorrhoea, gynaecomastia.

General disorders and administration site conditions:

Common: fatigue, weakness, sweating, clammy hands;
Uncommon: fever, malaise, oedema, facial oedema;
Rare: cold intolerance.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

In healthy normal human subjects, the maximum tolerated dose of buspirone hydrochloride is 375 mg/day. As the maximum dose levels were approached, the most commonly observed symptoms were: nausea, vomiting, dizziness, drowsiness, miosis and gastric distress. No deaths have been reported in humans with deliberate or accidental overdosage of buspirone alone. Toxicology studies of buspirone yielded the following LD_{50} values : mice, 655 mg/kg; rats, 196 mg/kg; dogs, 586 mg/kg; and monkeys, 356 mg/kg.

Treatment

General symptomatic and supportive measures should be used. Activated charcoal may reduce absorption of the medicine if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Respiration, pulse and blood pressure should be monitored as in all cases of drug overdosage. No specific antidote is known for buspirone. Dialysis does not modify the blood levels of buspirone in anuric patients. The buspirone metabolite 1-pyrimidinylpiperazine (1-PP) is partially removed by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Buspirone hydrochloride is an antianxiety agent that is not chemically or pharmacodynamically related to benzodiazepines, but has some resemblance to drugs which interact with dopamine receptors. It belongs chemically to the class of pharmacologic agents with selective anxiolytic psychotropic activity known as the azapirones. ATC code N05BE01.

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 ($5\text{-}HT_{1A}$) 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.

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Buspirone is rapidly absorbed in humans and undergoes extensive first pass metabolism. Peak plasma levels are attained 60 to 90 minutes after ingestion. However, in some normal individuals, C_{max} may occur after several hours. Hepatic cirrhosis can delay C_{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 ng/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 humans, approximately 95% of buspirone is plasma protein bound, but other highly bound drugs, e.g. phenytoin, propranolol and warfarin, are not displaced by buspirone from plasma 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 humans, 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 14 evaluated 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 Contraindications** and **4.4 Special warnings and precautions for use**)

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_{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 Dose and method of administration**).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ANKSILON 5 mg and 10 mg tablets also contain lactose monohydrate, sodium starch glycollate type A, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See also section **4.5 Interactions with other medicines and other forms of interactions.**

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in original container to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

ANKSILON 5 mg tablets are supplied in PVC/PVDC/Al blister packs of 60 or 100 tablets enclosed in a carton.

ANKSILON 10 mg tablets are supplied in PVC/PVDC/Al blister packs of 60 or 100 tablets enclosed in a carton.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

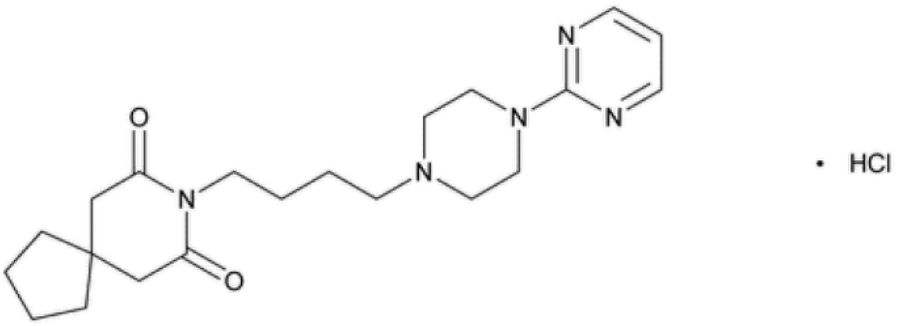
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Buspirone hydrochloride is a white, crystalline, water soluble compound with a molecular weight of 422.0 g/mol.

Chemical structure

Buspirone hydrochloride is chemically 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione monohydrochloride. The chemical structure is:



CAS number

33386-08-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Orion Pharma (Aus) Pty Limited
Level 24, Tower 3, 300 Barangaroo Avenue
Sydney NSW 2000, Australia
Telephone: 1800 861 913

9. DATE OF FIRST APPROVAL

16 January 2025

10. DATE OF REVISION

Not applicable

Summary table of changes

Section changed	Summary of new information
N/A	First PI for this medicine.