SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buspirone hydrochloride 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of buspirone (as hydrochloride).

Excipients with known effect:
Each 5 mg tablet contains 75.840 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White ovoid rectangular uncoated tablet with score line one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Buspirone is indicated for the treatment of short-term management of anxiety disorders and the relief of symptoms of anxiety with or without accompanying symptoms of depression.

4.2 Posology and method of administration

Posology
The dosage should be individualised for each patient.

Adults (including older people):
The usual starting dosage is 5 mg given two to three times per day. The dosage may be increased every 2-3 days. The usual therapeutic dosage is 15 to 30 mg daily in divided doses. The maximum recommended dose is 45mg daily 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. If buspirone is administered with a potent CYP3A4 inhibitor, the initial dose should be lowered and only increased gradually after

medical evaluation (see section 4.5).

Grapefruit juice increases the plasma concentrations of buspirone. Patients taking buspirone should avoid consuming large quantities of grapefruit juice.

Patients with Renal impairment
After a single administration to patients with mild to moderate renal insufficiency (creatinin clearance 20-49 ml/min/1.72 m^2) a slight increase in the buspirone blood levels was seen, without increase of the half-life time. In these patients buspirone should be administered with caution and a low dosage, two-times daily, is advised. The response and the symptoms of the patients should be evaluated carefully, before an eventual increase of the dosage is made. A single administration to anuretic patients causes an increase in the blood levels of the metabolite 1-pyrimidine/piperazine (1-PP), in which dialysis did not prove to have any influence on the buspirone levels, neither on the 1-PP levels. Buspirone should not be administered to patients with a creatinin clearance < 20 ml/min/1.72 m^2), especially not to anuretic patients, because of the fact that increased and untreated levels of buspirone and its metabolites may occur.

Patients with Hepatic impairment
As may be expected agents as buspirone used in patients with a reduced liver function show a reduced “first pass effect”. After a single administration to patients with liver cirrhosis, higher maximum concentrations of unchanged buspirone are seen, with an increase in the half life time. In these patients buspirone should be used with caution and individual dosages should be titrated with care to reduce the chance of central undesirable effects, which may occur because of high maximum concentrations of buspirone. Increased dosages should be considered carefully and only after 4-5 days experience with the prior dosage.

Pediatric population
Placebo-controlled trials, in which 334 patients were treated with buspirone for up to six weeks, have not shown buspirone at doses recommended for adults to be an effective treatment for generalised anxiety disorder in patients less than 18 years.

Plasma concentrations of buspirone and its active metabolite were higher in paediatric patients, compared to adults given equivalent doses (see section 5.2).

Method of administration

For oral administration.

4.3 Contraindications

Buspirone is contraindicated in the following groups of patients:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- patients with epilepsy.
- acute intoxication with alcohol, hypnotics, analgesics, or antipsychotic drugs.
- patients with severe renal or hepatic impairment. Severe renal impairment can be defined as a creatinine clearance of 20ml/min or below, or a plasma creatinine above 200µmol/l.

4.4 Special warnings and precautions for use

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 a MAOI. Therefore, it is

recommended that buspirone not be used concomitantly with a MAOI.

Buspirone should be used with care in the following situations:

- acute narrow-angle glaucoma
- myasthenia gravis
- drug dependence
- patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency or glucose – galactose malabsorption should not take this medicine.
- patients with a history of renal or hepatic impairment.
- alcohol use should be avoided, although buspirone has not been reported to potentiate the psychomotor impairment produced by alcohol. No data are available on concomitant use of alcohol and single doses of buspirone greater than 20 mg.
- buspirone does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic agents. It will not block the withdrawal syndrome often seen with cessation of therapy with these agents. Patients should be gradually withdrawn from these agents before initiating buspirone treatment.

  Buspirone should not be used alone to treat depression, and may potentially mask the clinical signs of depression.

  Paediatric population
  The long-term safety and effectiveness of buspirone have not been determined in individuals below 18 years of age. Buspirone is not recommended in children and adolescents (see section 4.2).

  Drug abuse and dependence
  Buspirone is not a controlled substance.

  Buspirone has shown no potential for drug abuse and dependence based on human and animal studies.

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

  Long-term toxicity
  Because its mechanism of action is not fully elucidated, long-term toxicity in the CNS or other organ systems cannot be predicted.

  Lactose
  Buspirone tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorption should not take Buspirone tablets.

4.5 Interaction with other medicinal products and other forms of interaction

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

<u>Effect of other drugs on buspirone</u>

Association not recommended:

MAO inhibitors: Co-administration of MAO inhibitors may cause increases in blood pressure. Co-administration of MAO inhibitors and buspirone is therefore not recommended (see section 4.4).

Erythromycin: Concomitant administration of buspirone (10 mg as single dose) and erythromycin (1.5 g once daily for four days) in healthy volunteers increased the plasma concentrations of buspirone (C_{max} increased 5-fold and AUC 6-fold). If buspirone and erythromycin are to be used in combination, a low dose of buspirone (e.g., 2.5 mg twice daily) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Itraconazole: Concomitant administration of buspirone (10 mg as single dose) and itraconazole (200 mg once daily for four days) in healthy volunteers increased the plasma concentrations of buspirone (C_{max} increased 13-fold and AUC 19-fold). If buspirone and itraconazole are to be used in combination, a low dose of buspirone (e.g., 2.5 mg once daily) is recommended. Subsequent dose adjustments of either drug should be based on clinical response.

Association with precautions of use:

Diltiazem: Concomitant administration of buspirone (10 mg as single dose) and diltiazem (60 mg three times daily) in healthy volunteers increased the plasma concentrations of buspirone (C_{max} increased 5.3-fold and AUC 4-fold). 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: Concomitant administration of buspirone (10 mg as single dose) and verapamil (80 mg three times daily) in healthy volunteers increased the plasma concentrations of buspirone (C_{max} and AUC 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: Rifampicin induces the metabolism of buspirone via CYP3A4. Therefore, concomitant administration of buspirone (30 mg as single dose) and rifampicin (600 mg once daily for 5 days) in healthy volunteers decreased the plasma concentrations (C_{max} decreased 84 % and AUC decreased 90 %) and the pharmacodynamic effect of buspirone.

- Antidepressants - the occurrence of elevated blood pressure in patients receiving buspirone and monoamine oxidase inhibitors (phenelzine and tranylcypromine) has been reported. Buspirone should not be used concomitantly with a MAOI. In healthy volunteers no interaction with the tricyclic antidepressant amitriptyline was seen.
- Baclofen, lofexidine, nabilone, antihistamines may enhance any sedative effect.

Association to be taken into account:

SSRI: The combination of buspirone and selective serotonin reuptake inhibitors (SSRI)

was tested in a number of clinical trials on more than 300,000 patients. Although no severe toxicities were observed, there were rare cases of seizures in patients that took SSRI and buspirone concomitantly.

Separate cases of seizures in patients administered combination therapy with buspirone and SSRIs have been reported from regular clinical use. Buspirone should be used with caution in combination with serotonergic drugs (including MAOIs, L-tryptophan, triptans, tramadol, 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.

Protein Binding: In vitro buspirone may displace less firmly protein-bound drugs like digoxin. The clinical significance of this property is unknown.

Nefazodone: The coadministration of buspirone (2.5 or 5 mg twice daily) and nefazodone (250 mg twice daily) to healthy volunteers resulted in marked increases in plasma buspirone concentrations (increases up to 20-fold in C_{max} and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of buspirone metabolite, 1- pyrimidinylpiperazine. With 5-mg twice daily 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 twice daily and nefazodone 250 mg twice daily was similar to that for subjects receiving either drug alone. Subjects receiving buspirone 5 mg twice daily and nefazodone 250 mg twice daily 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.

Grapefruit juice: Concomitant administration of buspirone 10 mg and grapefruit juice (double strength 200 ml for 2 days) in healthy volunteers increased the plasma concentrations of buspirone (C_{max} increased 4.3-fold and AUC 9.2-fold).

Other Inhibitors and Inducers of CYP3A4: When administered with a potent inhibitor of CYP3A4, a low dose of buspirone, used cautiously, is recommended. When used in combination with a potent inducer of CYP3A4, e.g. phenobarbital, phenytoin, carbamazepine, St. John's wort, an adjustment of the dosage of buspirone may be necessary to maintain busprione's anxiolytic effect.

Fluvoxamine: In short-term treatment with fluvoxamine and buspirone doubled buspirone plasma concentrations are observed compared to mono- therapy with buspirone.

Trazodone: Concomitant administration of trazodone showed a 3-6 fold increase of ALT in some patients.

Cimetidine: The concomitant use of buspirone and cimetidine has shown a slight increase in the 1-(2-pyrimidinyl)-piperazine metabolite of Buspirone. Because of the high protein binding of Buspirone (around 95%) caution is advised when drugs with a high protein binding are given concomitantly.

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

In vitro studies have shown that buspirone does not displace warfarin, digoxin, phenytoin, or propranolol from plasma proteins.

Effect of buspirone on other drugs

Diazepam: After addition of buspirone to the diazepam dose regimen, no statistically significant differences in the steady-state pharmacokinetic parameters (C_{max}, AUC, and C_{min}) were observed for diazepam, but increases of about 15% were seen for nordiazepam, and minor adverse clinical effects (dizziness, headache, and nausea) were observed.

Haloperidol: Concomitant administration of haloperidol and buspirone can increase haloperidol serum levels.

Digoxin: In humans, approximately 95% of buspirone is plasma protein bound. *In vitro*, buspirone does not displace tightly bound drugs (*ie* warfarin) from serum proteins. However, *in vitro*, buspirone may displace less firmly protein-bound drugs like digoxin. The clinical significance of this property is unknown.

There are reports on increases in the prothrombin time after the addition of buspirone to a treatment regimen containing warfarin.

4.6 Fertility, pregnancy and lactation

In some studies, administration of high doses of buspirone to pregnant animals produced effects on survival, birth and weaning weights, although there was no effect on foetal development. Since the relevance of this finding in humans has not been established, buspirone is contraindicated in pregnancy and in lactation.

4.7 Effects on ability to drive and use machines

Buspirone has moderate influence on the ability to drive and use machines. Attention is drawn to the risks associated with drowsiness or dizziness induced by this drug (see section 4.8).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive
• Do not drive until you know how the medicine affects you
• It is an offence to drive while under the influence of this medicine
• However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and it was not affecting your ability to drive safely.

4.8 Undesirable effects

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.

Clinical experience
When patients receiving buspirone were compared with patients receiving placebo, dizziness, headache, nervousness, lightheaded-ness, 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.

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

ADVERSE DRUG EVENTS REPORTED DURING CLINICAL EXPERIENCE

System Organ Class	**Frequency**	**MedDRA Terms**
Psychiatric Disorders	common	nervousness, insomnia, disturbance in attention, depression, confusional state, sleep disorder, anger
	very rare	psychotic disorder, hallucination, depersonalization, affect lability
Nervous System Disorders	very common	dizziness*, headache, somnolence
	common	paraesthesia, vision blurred, coordination abnormal, tremor, tinnitus
	very rare	serotonin syndrome, convulsion, tunnel vision, extrapyramidal disorder, cogwheel rigidity, dyskinesia, dystonia, syncope, amnesia, ataxias, Parkinsonism, akathisia, restless leg syndrome, restlessness
Cardiac Disorders	common	tachycardia, chest pain
Respiratory, Thoracic and Mediastinal Disorders	common	nasal congestion, pharyngolaryngeal pain
Gastrointestinal Disorders	common	nausea, abdominal pain, dry mouth, diarrhoea, constipation, vomiting
Skin and Subcutaneous Tissue Disorders	common	cold sweat, rash
	rare	angioneurotic oedema, ecchymosis, urticaria
Musculoskeletal and Connective Tissue Disorders	common	musculoskeletal pain
Renal and Urinary Disorders	very rare	urinary retention
Reproductive System and Breast Disorders	very rare	galactorrhoea

General Disorders and Administration Site Conditions	common	fatigue

* Dizziness includes lightheadedness.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Features:
In normal volunteers, the maximum tolerated dose of buspirone was 375 mg/day. As the maximum dose levels were approached, the most commonly observed symptoms include nausea, vomiting, headache, dizziness, drowsiness, tinnitus, restlessness, miosis, and gastric distress. Mild bradycardia and hypotension have been reported. Extrapyramidal symptoms have been reported after therapeutic doses. Rarely convulsions may occur.

There is no specific antidote to buspirone. Buspirone is not removed by haemodialysis. The stomach should be emptied as quickly as possible. Treatment should be symptomatic and supportive. The ingestion of multiple agents should be suspected.

Management:
Treatment should by symptomatic and supportive. The benefit of gastric decontamination is uncertain. Consider activated charcoal if the patient presents within 1 hour of ingestion of more than 5mg/kg provided they are not too drowsy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Azaspirodecanedione derivatives, ATC code: N05B E01

Buspirone is an azaspirodecanedione. The exact mechanism of buspirone anxioselective action is not fully known. It does not act on benzodiazepine receptor sites and lacks sedative, anticonvulsant and muscle relaxant properties. From animal studies it is known to interact with serotonin, noradrenaline (norepinephrine), acetylcholine and dopamine systems of the brain. Buspirone enhances the activity of specific noradrenergic and dopaminergic pathways, whereas the activity of serotonin and acetylcholine are reduced.

5.2 Pharmacokinetic properties

Absorption
Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 40 to 90 minutes after administration by mouth. Systemic bioavailability is low because of extensive first-pass metabolism.

Distribution

Buspirone is about 95% bound to plasma proteins.

Metabolism:
Metabolism in the liver is extensive via the cytochrome P450 isoenzyme CYP3A4. The elimination half-life of buspirone is usually about 2 to 4 hours but half-lives of up to 11 hours have been reported.

Elimination:
Buspirone is excreted mainly as metabolites in the urine, and also the faeces.

At steady state, the following doses of buspirone in children aged 6–12 years resulted in increases in C_{max} (maximum concentration) and AUC (area under the curve), compared with adults, as shown in the table:

Dosage	**C_{max}**	**AUC**
7.5 mg b.i.d	2.9 – fold	1.8 – fold
15 mg b.i.d	2.1 – fold	1.5 – fold

Across the dose range studied, the C_{max} and AUC of 1-PP (the active metabolite of buspirone, 1-pyrimidinylpiperazine) in children were approximately double those in adults.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose (Aavicel-PH-101)
Sodium starch glycolate
Microcrystalline cellulose (Aavicel-PH-200)
Colloidal silicon dioxide
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The product is supplied in blister packs of white opaque PVC film and plain aluminium blister foil.

Blister pack sizes: 20, 30, 40, 50, 60, 90 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Arcolab International Ltd.
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Tolpits Lane, Watford,
Hertfordshire WD18 9SS
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 28176/0153

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10 DATE OF REVISION OF THE TEXT

20/09/2017