SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buspar Tablets 10MG.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: buspirone hydrochloride 10mg.

3 PHARMACEUTICAL FORM

Oral tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The dosage should be individualized for each patient

Adults (including the elderly): the usual starting dosage is 5mg given two to three times per day. The dosage may be increased every 2-3 days. The usual therapeutic dosage is 15 to 30mg 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.

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.

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.

Children:
Placebo-controlled trials, in which 334 patients were treated with buspirone for up to six weeks, have not shown buspirone at doses recommended for adult 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 5.2, Pharmacokinetic Properties.)

Method of Administration
For oral administration

4.3 Contraindications

Buspirone is contraindicated in the following groups of patients.

- patients with known hypersensitivity to buspirone hydrochloride or any ingredient in the tablet.
- 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 20mg.
- 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 use
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.

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.

Effect of other drugs on buspirone
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 (Cmax 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 (Cmax 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 (Cmax 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 (Cmax 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 (Cmax 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 (Cmax 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

There are no or limited amount of data from the use of buspirone in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of buspirone during pregnancy.

The effect of buspirone on labour and delivery is unknown.

It is unknown whether buspirone or its metabolite/metabolites are excreted in human milk.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from buspirone therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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, <1/10), and very rare (<1/10000).

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 Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

ATC code NO5B E01

Buspar is an azaspirodecanedione. The exact mechanism of Buspar 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, acetylcholine and dopamine systems of the brain. Buspar enhances the activity of specific noradrenergic and dopaminergic pathways, whereas the activity of serotonin and acetylcholine are reduced.

5.2 Pharmacokinetic properties

Buspar is rapidly absorbed when given orally. It is then subject to considerable first-pass metabolism. Peak plasma levels occur 60-90 minutes after dosing. Plasma concentration is linearly related to dose. Following multiple dosing steady state plasma concentrations are achieved within 2 days.

Buspar is 95% protein bound. Buspar is eliminated primarily by liver metabolism. In pharmacokinetic studies mean plasma half-lives varied from 2 to 11 hours.
At steady state, the following doses of buspirone in children aged 6-12 years resulted in increases in Cmax (maximum concentration) and AUC (area under the curve), compared with adults, as shown in the table:

Dosage	Cmax	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 Cmax and AUC of 1-PP (the active metabolite of buspirone, 1-pyrimidinylpiperazine) in children were approximately double those of 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, sodium carboxymethyl starch, microcrystalline cellulose, silicon dioxide colloidal, magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The tablets are packed in bottles containing 50 or 100 tablets; blisters containing 21, 30, 56, 60, 84 & 90 tablets.

6.6 Special precautions for disposal

No specific instructions.

7 MARKETING AUTHORISATION HOLDER

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