SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buspirone hydrochloride 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg of buspirone hydrochloride.

Excipient with known effect:
Each tablet contains 111.4 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablet can be divided into equal doses.

Buspirone hydrochloride 10 mg tablets are white, capsule shaped tablets, embossed “BR (breakline) 10” on one side, “G” on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Buspirone hydrochloride tablets are indicated for short-term treatment of general anxiety disorders and to relieve the 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.

Food increases the bioavailability of buspirone. 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 (see section 4.5).

Adults (including the elderly):
Initially, a dose of 5 mg two to three times daily is given. After several weeks, to allow for a lag period, this may be increased in increments of 5 mg at 2 to 3 day intervals according to the therapeutic response. After dosage titration, the usual daily dose is 15 to 30 mg per day in divided doses. The maximum recommended dose should not exceed 60 mg per day.

Older people:
Current data do not support a change in dosage regimen based on age or sex of the patient.

Paediatric population:
The therapeutic use of buspirone in children has not been established. 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).

Renal impairment:
After a single administration to patients with mild to moderate renal insufficiency (creatinin clearance 20-49 ml/min/1,72m^2) a slight increase in the buspirone blood levels was seen, without increase of the half-life time. In these patients buspirone hydrochloride Tablets 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 Hydrochloride Tablets 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.

<u>Method of administration</u>
For oral use.
Buspirone should be taken at the same time each day and consistently with or without food. Tablets should be taken with some fluid and should not be chewed.

4.3 Contraindications

Buspirone hydrochloride is contraindicated in:

- Hypersensitivity to the active substance or to any excipients listed in section 6.1.
- Severe renal (defined as creatinine clearance <20 ml/min/1.72 m^2 or a plasma creatinine above 200 micromoles/litre) or severe hepatic insufficiency.
- Acute intoxication with alcohol, hypnotics, analgesics or antipsychotic drugs.
- Patients with epilepsy.

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 caution in patients with:

- Acute narrow-angle glaucoma.
- Myasthenia gravis.
- Drug dependence.
- History of hepatic or renal 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 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).

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.

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.

Cases of insomnia, anxiety, agitation, depersonalisation and paraesthesias are seen in a few patients on discontinuation of the therapy.

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.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 (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 MAO inhibitor. In healthy volunteers no interaction with the tricyclic antidepressant amitriptyline was seen.

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.

Cytochrome P450 3A4
Buspirone is metabolised by CYP 3A4. In vivo studies showed interactions with the strong inhibitors like Nefazodone, Erythromycin, Itraconazole and Verapamil. Dose adaptation should be considered in the case of buspirone is co-administered with strong CYP3A4 inhibitors like HIV protease inhibitors or Ketoconazole. Further dose adjustment should be based on clinical effects.

Nefazodone:
The co-administration 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 Cmax 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 Cmax 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). Patients using buspirone are advised to avoid drinking grapefruit juice.

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 buspirone'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 warfarin, phenytoin or propranolol are not displaced from plasma proteins by buspirone.

Effect of buspirone on other drugs
Because of the high protein binding of buspirone (around 95%) caution is advised when drugs with a high protein binding are given concomitantly.

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

Haloperidol:
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

Pregnancy
There are no or limited amount of data from the use of buspirone in pregnant women. Adverse effects have been reported only after the administration of high doses of the drug. 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.

Breastfeeding
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 patients 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 prescribled to treat a medical or dental problem and
- You have taken it according to the instruction 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

Undesirable effects most frequently reported include dizziness, headache, light-headedness, nausea, nervousness, excitement, sweating and clamminess. Side effects, if they occur, are generally observed at the beginning of treatment and usually subside or disappear as treatment progresses and/or with dose lowering.

Clinical experience

When patients receiving buspirone were compared with patients receiving placebo, dizziness, headache, nervousness, lightheadedness, 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), rare (≥ 1/10,000 to < 1/1,000) and very rare (<1/10,000).

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, excitement.
	very rare	psychotic disorder, hallucination, depersonalization, affect lability.
Nervous System disorders	very common	dizziness*, headache, somnolence, drowsiness,
	common	Paraesthesia/numbness, coordination abnormal, coordination disturbances, tremor.
	very rare	serotonin syndrome, convulsion, extrapyramidal disorder, cogwheel rigidity, dyskinesia, dystonia, syncope, amnesia, ataxias, Parkinsonism, akathisia, restless leg syndrome, restlessness
Eye disorders	common	blurred vision.
	very rare	tunnel vision.
Ear and labyrinth disorders	common	tinnitus.
Cardiac disorders	common	tachycardia, chest pain, palpitations
Respiratory, thoracic and mediastinal disorders	common	nasal congestion, nasal stuffiness, throat pain, 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, pruritus, alopecia
Musculoskeletal and connective tissue disorders	common	musculoskeletal pain
Renal and urinary disorders	very rare	urinary retention
Reproductive system and breast disorders	very rare	galactorrhoea

ADVERSE DRUG EVENTS REPORTED DURING CLINICAL EXPERIENCE		
System Organ Class	**Frequency**	**MedDRA Terms**
General disorders and administration site conditions	common	fatigue/weakness

* 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).

4.9 Overdose

Symptoms
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 were 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.

Management
Treatment should be symptomatic and supportive. The ingestion of multiple agents should be suspected. 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. No specific antidote exists. Buspirone hydrochloride is not removed by haemodialysis . The stomach should be emptied as quickly as possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, azaspirodecanedione derivatives, ATC code: NO5B E01

Buspirone is a member of the azapirone class of drugs. It has anxiolytic activity, but is largely lacking in sedative and muscle relaxant effects and anticonvulsant activity.

Its mechanism of action has yet to be fully explained. It does not act on benzodiazepine receptor sites and lacks sedative, anticonvulsant and muscle relaxant properties. Evidence to date suggests that its activity is based on its effects on serotonin (5-HT) receptors. It acts as an agonist of pre-synaptic and partial agonist of post-synaptic 5-HT_{1A} subtype receptors. It

is thought this initiates long-term changes in central 5-HT neurotransmission, producing the efficacy seen in the treatment of anxiety. Buspirone is thought to have antagonist activity at D_2 receptors at the doses stipulated for anxious disorders, though it is unclear if this is linked to its anxiolytic activity.

Buspirone's effects on GABAergic mechanisms are unclear. It does not directly interact with either the benzodiazepine-GABA receptor complex or GABA receptors. However, there is indirect evidence for buspirone having a GABA antagonist-like action.

The onset of action can take 1-3 weeks and the full effect beyond 4 weeks has not been demonstrated.

From animal studies it is known to interact with serotonin, noradrenaline, 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.

There has been no evidence of pharmacodependence in studies performed in animals and on humans.

5.2 Pharmacokinetic properties

Absorption
Buspirone hydrochloride is rapidly absorbed from the gastrointestinal tract and undergoes extensive pre-systematic metabolism (bioavailability 4%). Peak plasma levels are noted at approximately 60 minutes after oral administration range 30-150 minutes. Plasma concentration is related linearly to the dose given. Concomitant administration of food slows absorption slightly. Whilst this decreases pre-systematic metabolism, it is not deemed clinically significant. Systemic bioavailability is low because of extensive first-pass metabolism.

Distribution
Equilibrium of plasma levels is reached after 3-5 days of repeated dosing, with around 95% bound to plasma proteins.

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 of adults.

Biotransformation
Buspirone hydrochloride is extensively metabolised in the liver by cytochrome P450 3A4 to two main metabolites: 1-(2-pyrimidinyl)-piperazine and 5-hydroxybuspirone. 1-(2-pyrimidinyl)-piperazine is pharmacologically active with approximately 20% of the potency of buspirone, though it is unclear if it has any effect on buspirones overall anxiolytic action. The latter is present as both free and glucoroconjugated forms.

Elimination
The apparent plasma half-life for the elimination of buspirone is 2 to 3 hours, range 1.5 - 7 hours with the elimination of the metabolites: 1-(2-pyrimidinyl)-piperazine and 5-hydroxybuspirone and its glucuronide taking a little longer.

Elimination occurs mainly as metabolites in the urine and faeces and takes place largely in the first 24 hours following administration.

5.3 Preclinical safety data

Toxicity studies in several animal species have shown little evidence of undesirable effects, with toxic effects occurring only at levels well in excess of those recommended for clinical use.

No adverse effects have been described when buspirone hydrochloride has been tested *in vitro* and *in vivo* for carcinogenicity, mutagenicity and teratogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose, microcrystalline
Sodium starch glycolate Type A
Silica, colloidal anhydrous
Magnesium stearate

6.2. Incompatibilities

Not applicable.

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

HDPE tablet containers fitted with polypropylene caps and optional styrene wad in packs of 5, 7, 10, 15, 20, 21, 25, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 250 or 500 tablets.

PVC (250 μm) aluminium blister strips placed in cardboard cartons.

PVC/PVdC (285 μm) aluminium blister strips placed in cardboard cartons.

Blister strips will be available in packs of 20, 28, 30, 50, 56, 84, 90, 100, 112, 120, 168, or 180 tablets.

6.6 Special precautions for disposal and other handling

Not Applicable.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0369

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