# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Buspirone hydrochloride 10 mg tablet

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dosage form contains 10 mg buspirone hydrochloride.

Excipients with known effect:

10 mg tablet: each tablet contains 66 mg Lactose (as monohydrate).

For the full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Oral tablet.

Round white to off-white tablets plain from both sides.

## 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 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 30 mg daily in divided doses. The maximum recommended dose is 60mg 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 (see section 4.5).

*Renal impairment*
After a single administration to patients with mild to moderate renal insufficiency (creatinine 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 creatinine 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.

Elderly Patients

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

*Paediatric 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 generalized 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:

• patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• patients with severe renal (defined as creatinine clearance of 20 ml/min or below, or a plasma creatinine above 200 μmol/l) or severe hepatic impairment.
• 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 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 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
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Serotonin Syndrome
Concomitant administration of buspirone and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

## 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 (phenelzine and tranylcypromine) 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), probably due to CYP3A4 inhibition. 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), probably due to CYP3A4 inhibition. 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), probably due to inhibition of CYP3A4 first-pass metabolism. 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), probably due to inhibition of CYP3A4 first-pass metabolism. 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 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 $C_{max}$ 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 (e.g. 2,5 mg twice daily). 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*:

*In vitro* studies have shown that buspirone is metabolized by cytochrome P450 3A4 (CYP3A4). When administered with a potent inhibitor of CYP3A4, a low dose of buspirone (such as 2.5mg twice daily), should be, used cautiously.

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 monotherapy 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.

*In vitro* studies have shown that warfarin, digoxin, phenytoin or propranolol are not displaced from plasma proteins by buspirone.

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

**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 (i.e. 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 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.

Breast-feeding
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 to <1/10), 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 |
| | 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, extrapyramidaldisorder, cogwheel rigidity, dyskinesia, dystonia, syncope, amnesia, ataxias, Parkinsonism,akathisia, restless leg syndrome, restlessness |
| Eye disorders | common | vision blurred |
| | very rare | tunnel vision |
| Ear and labyrinth disorders | common | tinnitus |
| 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 light headedness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

Recommended overdose treatmentIn 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. No specific antidote exists. Buspirone hydrochloride is not removed by haemodialysis. The stomach should be emptied as quickly as possible. The ingestion of multiple agents should be suspected.

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.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, azaspirodecanedione derivatives, ATC code: N05B 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. 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-HT1A 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 D2 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.

There has been no evidence of pharma codependence 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 first pass metabolism with only about 4% of a dose reaching systemic circulation. Peak plasma levels are noted between 60 and 90 minutes after oral administration. Plasma concentration is related linearly to the dose given.

Concomitant administration of food slows absorption slightly. Whilst this decreases pre-systemic metabolism, it is not deemed clinically significant.

Distribution

Equilibration of plasma levels is reached after 2 days of repeated dosing, with around 95% bound to plasma proteins.

Biotansformation

Buspirone hydrochloride is extensively metabolised 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 buspirone's overall anxiolytic action. The latter is present as both free and glucuroconjugated forms.

Elimination

The apparent plasma half-life for the elimination of buspirone hydrochloride is 2 to 11 hours. Elimination occurs mainly in the urine (29 to 63% of the dose) and bile (18 to 38% of the dose). Elimination occurs mainly as metabolites and takes place largely in the first 24 hours following administration.

Paediatric population

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.

### 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

Cellulose, Microcrystalline pH 102

Cellulose, Microcrystalline pH 101

Lactose Monohydrate

Sodium Starch glycolate

Silica, Colloidal anhydrous

Magnesium Stearate

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

36 months

## 6.4 Special precautions for storage

Store in the original package.

## 6.5 Nature and contents of container

*Blisters:*
Transparent PVC/PVDC/Alu blisters, each containing 10 tablets
Blister pack sizes: 30 tablets per pack

## 6.6 Special precautions for disposal

There are no special instructions for use/handling.

# 7 MARKETING AUTHORISATION HOLDER

Rivopharm UK Limited
100 Bishopsgate
London
EC2N 4AG
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 33155/0121

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/06/2024

## 10 DATE OF REVISION OF THE TEXT

14/06/2024