ABSTRACTED PRESCRIBING INFORMATION PREPARED FROM NCDS-V02 (20 AUGUST 2012):

BUSPAR Buspirone Hydrochloride

Indication: BUSPAR is indicated for the short term management of anxiety disorders, the relief of symptoms of anxiety with or without accompanying depression. Dosage and Administration: The maximum daily dosage should not exceed 45 mg per day. 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. Grapefruit juice increases the plasma concentrations of buspirone. Patients taking buspirone should avoid consuming large quantities of grapefruit juice. Route of Administration: For oral use. Adults: Dosage should be adjusted according to response for optimal efficacy and safety. The recommended initial dose is 5 mg two to three times daily and this may be increased every two to three days. The usual therapeutic dose is 15 to 30 mg daily in divided doses with a maximum recommended dose of 45 mg daily in divided doses. 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 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 pediatric patients, compared to adults given equivalent doses. Elderly: Current data do not support a change in dosage regimen based on age or sex of the patient. Renal impairment: After a single administration to patients with mild to moderate renal insufficiency (creatinine clearance 20-49 ml/min/1.72 m2) 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 m2), 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 like 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. **CONTRAINDICATIONS:** Buspirone hydrochloride is contraindicated in: patients hypersensitive to buspirone hydrochloride or any of the excipients, severe renal (creatinine clearance <20 ml/min/1.72 m2 or a plasma creatinine above 200µmol/l) or severe hepatic insufficiency, acute intoxication with alcohol, hypnotics, analgesics, or antipsychotic drugs, patients with epilepsy. **WARNINGS AND PRECAUTIONS:** *Monoamine Oxidase Inhibitors:* 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. *Psychomotor functions:* In controlled studies in healthy volunteers, buspirone in single doses up to 20 mg caused no significant impairment of cognitive or psychomotor functions, unlike the benzodiazepines, diazepam or lorazepam. In studies in healthy volunteers, buspirone did not potentiate the psychomotor impairment produced by alcohol, in contrast to a comparative benzodiazepine. However, no data are available on concomitant use of alcohol and buspirone at single doses greater than 20 mg. It is prudent therefore to avoid alcohol while taking Buspirone. *Special precautions:* Buspirone should be used with caution in patients with: acute narrow-angle glaucoma, myasthenia gravis, drug dependence, hepatic or renal impairment. *Monotherapy:* 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. *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, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this product. *Drug interactions:* 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. **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. **Association to be taken into account: Selective Serotonin Reuptake Inhibitors (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. **Digoxin**: *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 Cmax and up to 50-fold in AUC) and statistically significant decreases (about 50%) in plasma concentrations of buspirone metabolite, 1-pyrimidinylpiperazine. With 5mg 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 (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 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. **Trazadone:** Concomitant administration of trazadone 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: Those drugs 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 (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. **Warfarin:** There are reports on increases in the prothrombin time after the addition of buspirone to a treatment
regimen containing warfarin. **Pregnancy and Lactation:** Fertility: There are no relevant data available. 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.

**Ability to perform tasks that require judgement, motor or cognitive skills:** Buspirone has a moderate influence on the ability to drive and use machines. Attention should be drawn to the risks associated with drowsiness or dizziness induced by this drug. **Adverse Reactions:**

*Psychiatric disorders:* **Common:** nervousness, insomnia, disturbance in attention, depression, confusional state, sleep disorder, anger. **Very rare:** psychotic disorder, hallucination, depersonalisation, 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, diarrhea, 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. **Overdose: Symptoms and signs:** 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, dizziness, drowsiness, miosis, and gastric distress. **Treatment:** 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. **Storage:** Store at temperature not exceeding 30°C. **Full Prescribing Information is available on request. Please read the full prescribing information prior to administration.**