SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buspirone 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg buspirone hydrochloride.

Excipient with known effect:

5 mg tablet: Each tablet contains 59.5 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

5 mg tablet:

White or almost white, oval tablets debossed with ‘ORN 30’ on one side and a score on the other side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for the symptomatic treatment of anxiety states of clinically relevant severity with the following cardinal symptoms: anxiety, agitation, tension.

4.2 Posology and method of administration

Posology

The dosage depends on the individual circumstances of the patient.

Adults (over 18 years of age)

At the start of the treatment 5 mg buspirone hydrochloride three times daily and this may be increased every two to three days

If necessary, the daily dose can be increased to 20-30 mg buspirone hydrochloride divided into several individual doses.

More than 60 mg buspirone hydrochloride per day should not be taken.

A single dose of 30 mg buspirone hydrochloride should not be exceeded.

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).

Due to latency of effect patients should be advised not to expect immediate benefit.

If there is no improvement of symptoms within 4-8 weeks, treatment with buspirone should be reconsidered. Treatment benefits and dose should be re-evaluated at regular intervals (see section 4.4).

Special patient groups

Renal impairment

In patients with renal impairment (creatinine clearance 20- 49 mL/min/ 1.72 m^2) 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. 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 levels of buspirone and its metabolites may occur (see sections 4.3, 4.4 and 5.2).

Hepatic impairment

In patients with hepatic impairment 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 (see sections 4.4 and 5.2). Buspirone is contraindicated in patients with severe hepatic impairment (see section 4.3).

Age and gender

Current data do not support any modification of the patient's dosage regimen based on age or gender.

Paediatric patients

Buspirone should not be used in children and adolescents under 18 years of age as the safety and efficacy of buspirone in this age group have not been established (see sections 5.1 and 5.2).

Method of administration

Buspirone tablets can be divided into equal doses and must be swallowed with liquid. The bioavailability of buspirone is increased by food. Buspirone should be taken at the same time each day and consistently with or without food.

4.3 Contraindications

Buspirone should not be administered in case of:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- acute angle-closure glaucoma
- myasthenia gravis
- epilepsy
- acute intoxication with alcohol, hypnotics, analgesics, or antipsychotic drugs
- severe hepatic insufficiency
- severe renal insufficiency (creatinine clearance <20 mL/min/1.72 m^2).

4.4 Special warnings and precautions for use

Note

Not all states of anxiety require medical treatment. They may also be a result of physical or mental illness and may sometimes be cured by targeted treatment of the underlying disease.

In clinical and experimental studies, there has been no indication that buspirone causes the risk of developing habituation or addiction. Nevertheless, until further clinical experience is gained, the administration should be monitored accordingly. Buspirone should be used with caution in patients with drug dependence.

Buspirone should be used with caution in patients with hepatic or renal impairment (see section 4.2).

Because buspirone has no cross-tolerance to benzodiazepines and other sedatives/hypnotics, it will not block the withdrawal symptoms that often occur at the discontinuation of these preparations. Therefore, before starting treatment with buspirone, these medicinal products should be discontinued gradually. This has particular relevance to patients who have taken a medicinal product with calming effect on the CNS for a long time. Careful observation is recommended for the use of buspirone in patients with a history of seizures.

In individual cases, seizures were reported when taking buspirone and SSRIs concurrently (see section 4.5).

A combination of buspirone with MAOIs is not recommended because of the risk of hypertensive reactions (see section 4.5).

The concomitant use of buspirone with other CNS-active drugs should be approached with caution (see section 4.5).

If a long-term medical treatment is necessary, it should be monitored intensively. The need to continue treatment should be periodically reassessed by discontinuation of treatment after a longer period of time (several months).

Psycho- and sociotherapeutic measures should not be neglected during the treatment with buspirone.

Since the mechanism of action of buspirone is not fully known, the long-term toxic effects on the central nervous system or other body systems cannot be predicted. Controlled clinical studies with buspirone have only been performed over a period of six months.

Paediatric population

Buspirone should not be used in children and adolescents under 18 years of age as the safety and efficacy have not been established in this age group (see sections 5.1 and 5.2).

Excipients

Buspirone tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

There are not sufficient data available regarding the concomitant use with other anxiolytics/sedatives and other centrally acting agents (e.g. antipsychotics and antidepressants), as well as antihypertensives, antidiabetics, anticoagulants, contraceptives and cardiac glycosides. Therefore, the concomitant use of buspirone with these medicinal products should be monitored carefully.

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 hydrochloride (10 mg as a 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), probably due to CYP 3A4 inhibition. If buspirone and erythromycin are to be used in combination, a low dose of buspirone hydrochloride (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 hydrochloride (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), probably due to CYP 3A4 inhibition. If buspirone and itraconazole are to be used in combination, a low dose of buspirone hydrochloride (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 hydrochloride (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), probably due to inhibition of CYP 3A4 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 hydrochloride (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), probably due to inhibition of CYP 3A4 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 hydrochloride (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.

Association to be taken into account:

SSRIs

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, buprenorphine, 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 hydrochloride (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, probably due to CYP 3A4 inhibition. With 5-mg twice daily doses of buspirone hydrochloride, 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 hydrochloride 2.5 mg twice daily and nefazodone 250 mg twice daily was similar to that for subjects receiving

either drug alone. Subjects receiving buspirone hydrochloride 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 hydrochloride 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 taking buspirone should avoid consuming large quantities of 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 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.

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 may enhance any sedative effect.

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

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.

Warfarin

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

Other CNS depressants

The sedative effect of buspirone may be enhanced if taken with other CNS depressants. Therefore, the concomitant use of buspirone with CNS depressant drugs should be monitored carefully.

The sedative effects of buspirone may be enhanced if taken with alcohol. Therefore the concurrent consumption of alcohol should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

In some animal studies, large doses of buspirone during pregnancy had adverse effects on survival and on birth and weaning weight, although there was no effect on foetal development. Since the relevance of this finding in humans has not been established, buspirone should be used only if clearly needed during pregnancy.

Breastfeeding

Available toxicological data in animals have shown excretion of buspirone (metabolite) in milk (for details see section5.3). A risk to the suckling child cannot be excluded. Lactation should therefore be discontinued during the treatment with buspirone.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

It cannot be excluded that buspirone - especially at the beginning of treatment and after a change in dose – but also by normal use affects the capacity of reaction to such extent that it has influence on the ability to drive and use machines.

Studies have shown that buspirone has less sedative effect than other anxiolytics, as it produces no significant psychomotor impairment. However, its effects on the individual patient's central nervous system are not predictable. Therefore, patients should be warned not to drive or to operate complex machinery until they are relatively sure that their performance is unimpaired by the use of buspirone.

4.8 Undesirable effects

The following frequency categories are used for classification of adverse reactions:

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)

Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders

Rare: blood count changes (eosinophilia, leukopenia, thrombocytopenia), bleeding disorders

Immune system disorders

Rare: allergic reactions

Endocrine disorders

Rare: thyroid dysfunction

Metabolism and nutrition disorders

Uncommon: increased appetite, anorexia, weight gain, weight loss

Psychiatric disorders

Common: nightmares, insomnia, nervousness, agitation, anger, hostility, confusion, depression

Uncommon: depersonalisation, euphoria, dysphoria, urge to move, anxiety, loss of interest, association disturbances, hallucinations, suicidal thoughts

Rare: mood swings, claustrophobia, psychosis, alcohol abuse

Nervous system disorders

Common:	headache, drowsiness, dizziness, light-headedness, impaired concentration
Uncommon:	numbness, abnormal sensations (e.g. tingling, pricking sensation), loss of coordination, tremors, seizures, roaring in the head, altered taste, drooling
Rare:	extrapyramidal symptoms including early and late dyskinesia, dystonia and rigidity, parkinsonism, akathisia, restless legs syndrome, slowed reaction time, involuntary movements, stupor, slurred speech, transient memory gaps, serotonin syndrome, loss of voice

Eye disorders

Common:	blurred vision
Uncommon:	redness of the eyes, itchy eyes, conjunctivitis
Rare:	eye pain, photophobia, sensation of pressure on the eyes, tunnel vision

Ear and labyrinth disorders

Common:	tinnitus
Uncommon:	hyperacusis

Cardiac disorders

Common:	nonspecific chest pain
Uncommon:	tachycardia/palpitations
Rare:	heart failure, heart attack, cardiomyopathy, bradycardia

Vascular disorders

Uncommon:	brief episodes of fainting, hypo- or hypertension
Rare:	cerebral blood flow disorders

Respiratory, thoracic and mediastinal disorders

Common:	sore throat, stuffy nose
Uncommon:	significantly increased breathing frequency, shortness of breath, chest pressure, altered sense of smell
Rare:	nosebleeds

Gastrointestinal disorders

Common:	nausea, dry mouth, gastrointestinal symptoms, diarrhoea
Uncommon:	rectal bleeding, constipation, flatulence, irritable colon, vomiting
Rare:	burning tongue, hiccups

Hepatobiliary disorders

Uncommon: increased liver enzymes

Skin and subcutaneous tissue disorders

Uncommon: urticaria, flushing, tendency to bruising, hair loss, dry skin, eczema, vesicula

Rare: small haemorrhages of the skin, acne, nail thinning

Musculoskeletal and connective tissue disorders

Uncommon: muscle cramps, muscle pain, muscle tension, joint pain

Rare: muscle weakness

Renal and urinary disorders

Uncommon: lower urinary tract symptoms

Rare: enuresis, nocturia

Reproductive system and breast disorders

Uncommon: menstrual disorders, decreased or increased libido

Rare: amenorrhea, pelvic inflammatory disease, abnormal ejaculation, impotence, galactorrhoea, gynaecomastia

General disorders and administration site conditions

Common: weakness

Uncommon: fever, malaise, fatigue, sweating, clammy hands, oedema, facial oedema

Rare: cold intolerance

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Mainly the following symptoms have been observed: nausea, vomiting, dizziness, fatigue, pupillary constriction and stomach complaints. Even with daily doses of up to 2,400 mg in humans, no serious complications were observed.

Therapeutic measures

In addition to general symptomatic treatment, an immediate gastric lavage should be performed in case of intoxication. As in any other cases of an overdose, breathing, pulse and blood pressure should be monitored. A specific antidote is not known. Buspirone is not removed by haemodialysis, the metabolite 1-PP is partially removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics; azaspirodecandione derivatives.

ATC code: N05BE01.

Buspirone represents the first anxiolytic of the class of active substances known as azaspirones. These are neither chemically nor pharmacologically related to benzodiazepines, barbiturates, or other psychotropic substances.

Buspirone is a complete agonist at presynaptic 5-hydroxytryptamine type-lA receptors and a partial agonist at postsynaptic 5-hydroxytryptamine type-lA receptors in the CNS.

Apparently the adaptive modulations of 5-HT neurotransmission play a key role in the anxiolytic effects of buspirone after repeated administration, which is why there is a delayed onset of action of 2-4 weeks.

The buspirone metabolite 1-[2-pyrimidinyl]-piperazine (1-PP) is a potent $\alpha 2$-antagonist, and as such it has an impact on the noradrenergic system, which can be associated with psycho-stimulatory and antidepressive effects.

The prevention of or dealing with stress-induced behavioural disorders may perhaps be considered as the fundamental characteristic of buspirone and other 5HT1A agonists. In a number of preclinical studies, buspirone had properties that are characteristic of anxiolytics and antidepressants.

Buspirone or 1-PP do not interact with the GABA-benzodiazepine receptor complex. In contrast to benzodiazepines, buspirone showed no signs of hypnotic-sedative, muscle relaxant, anticonvulsant, or alcohol abusive/addictive effects. In contrast to

benzodiazepines, it is unlikely that withdrawal symptoms or a rapid rebound of anxiety symptoms will occur after discontinuation of buspirone.

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 generalised anxiety disorder in patients less than 18 years.

5.2 Pharmacokinetic properties

Absorption

Buspirone is absorbed rapidly in humans following oral administration, however, the drug undergoes extensive first-pass metabolism with only about 4% of a dose reaching systemic circulation. Peak plasma levels are reached after 60-90 minutes; they were found to be a linear function of the administered dose over the entire therapeutic range.

Distribution

The plasma half-life is 2-3 hours. In plasma, more than 95% of the active ingredient is bound to proteins. Other drugs with high protein binding in blood, such as phenytoin, propranolol and warfarin, are not displaced by buspirone from plasma protein *in vitro* at clinically relevant buspirone concentrations. At higher concentrations, digoxin is displaced by buspirone *in vitro;* however, the clinical relevance of this finding is not clear.

Biotransformation

Buspirone is primarily metabolized by oxidation; the involvement of cytochrome P450 3A4 (CYP3A4) was demonstrated *in vitro*. Several hydroxylated derivatives and two pharmacologically active metabolites, 6-hydroxybuspiron (6-OHB) and 1-pyrimidinylpiperazin (1-PP), are produced.

In an animal study investigating the anxiolytic potential, 6-OHB displayed the same activity profile as buspirone.

In healthy volunteers, who received buspirone orally, the plasma concentrations of 6-OHB were approximately 40 times greater than those of buspirone, which leads to the suggestion that mainly this metabolite contributes to the clinical anxiolytic effects.

In animal studies, that have led to the conclusion of anxiolytic potential, the activity of 1-PP is approximately 25% or less compared to the activity of buspirone.

Elimination

The excretion of buspirone and its metabolites is approximately 29-63% in urine and 18-38% in faeces. The elimination of buspirone is reduced in patients with impaired hepatic or renal function. There were no significant differences in the pharmacokinetics of buspirone in relation to age or gender.

Renal impairment

After a single administration to patients with 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. 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.

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.

Paediatric population

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

5.3 Preclinical safety data

In studies with different animal species, a moderate acute toxicity of buspirone hydrochloride was determined. LD_{50} after oral treatment was 330 – 660 mg/kg BW in rats, 200 – 420 mg/kg BW in mice, about 300 mg/kg BW in dogs, and about 350 mg/kg BW in monkeys. Death mostly occurred immediately after administration of the drug and was accompanied by tonic-clonic seizures, body stiffness and other signs of CNS toxicity.

Studies of toxicity after repeated oral administration of buspirone hydrochloride in rats (up to 160 mg/kg BW/d) and mice (up to 200 mg/kg BW/day) showed dose-related weight loss. Tremor, hyperventilation and tachycardia were occasionally seen in rats, and amyloid deposits in the kidneys and the testicular tissue (ranging to testicular atrophy) and in the gastrointestinal tract were seen in mice.

After repeated oral administration of buspirone in monkeys, a dose-dependent mortality (> 50% at 100 mg/kg BW/day buspirone hydrochloride) and CNS toxicity was reported, including tremors, hypoactivity, catatonia, sedation and abnormal chewing movements.

Organ-specific toxic changes were not observed.

Reproductive toxicity studies in rats and rabbits revealed no evidence of teratogenic or fetotoxic effects of buspirone. In lactating rats, buspirone (metabolite) was excreted in the milk.

In *in vitro* and *in vivo* studies, buspirone showed no mutagenic or genotoxic effects.

Long-term studies showed no evidence of carcinogenic effects when buspirone hydrochloride was given to rats (up to 160 mg/kg BW/day for 2 years) and mice (up to 200 mg/kg BW/day for 18 months).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Silica, colloidal anhydrous

Cellulose, microcrystalline

Sodium starch glycolate (type A)

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

HDPE tablet container additionally:

After first opening: 1 year.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Blister additionally:

Keep the blister in the outer carton in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blister

20, 30, 50, 60, 90 and 100 tablets.

HDPE tablet container (60 mL) closed with a round child-resistant, tamper-evident PP screw cap (diameter 38 mm): 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Orion Corporation

Orionintie 1

FI-02200 Espoo

Finland

8 MARKETING AUTHORISATION NUMBER(S)

PL 27925/0068

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14/08/2012

Date of latest renewal: 20/06/2017

10 DATE OF REVISION OF THE TEXT

15/01/2021