IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0593/022/001
Case No: 2022410

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Stada Arzneimittel AG

Stadastrasse 2-18, **D-61118 Bad Vilbel**, **Germany**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Oxybutynin Stada 5 mg, tablet

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **16/02/2007** until **03/09/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxybutynin Stada 5 mg, tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxybutynin hydrochloride 5mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Tablets

White, round tablets, scored on both sides and marked 'OBC5' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Symptomatic treatment of detrusor overactivity (neurogenic or idiopathic detrusor overactivity) with the symptoms of urgency, frequency, and urge incontinence.

4.2 Posology and method of administration

The dosage should be individualised to disease severity and the patient's clinical response. As a rule, the lowest effective dose should be determined and used, taking account of the following dosage guidelines:

Adults:
1 Oxybutynin STADA 5 mg tablet 2-3 times a day (equivalent to 10–15mg of oxybutynin), starting with 2.5mg of oxybutynin 3 times a day. Oxybutynin STADA 5 mg should be taken in 2-3 (max.4) divided doses.

Elderly people:
Elderly people should be started on ½ Oxybutynin STADA 5 mg tablet twice daily (equivalent to 5mg of oxybutynin). Usually a dose of 10 mg in 2 divided doses may be sufficient, particularly if the patient is frail. In the elderly the elimination half life may be increased.

Children over 5 years of age:
Children over 5 years old should be started on ½ Oxybutynin STADA 5 mg tablet twice daily (equivalent to 5mg of oxybutynin). See table that follows for body weight-based maximum daily dose (0.3–0.4mg/kg body weight/day):

Table: Oxybutynin dosage

Age	**Daily dose**
5-9 yrs	7.5mg in 3 divided doses
9-12 yrs	10 mg in 2 divided doses
12 yrs and up (> 38 kg)	15 mg in 3 divided doses

The maximum recommended daily dose is 4 tablets (equivalent to 20mg of oxybutynin) for adults or 3 tablets (equivalent to 15mg of oxybutynin) for children.

The tablets should be swallowed whole with a drink of water.

The duration of therapy will be decided by the treating doctor.

4.3 Contraindications

– Hypersensitivity to oxybutynin hydrochloride or any other ingredient of the product

– Angle-closure glaucoma or any other condition associated with decreased aqueous outflow (e.g. narrow anterior chamber angles)

– Obstructive uropathy (e.g. prostatic hypertrophy or urethrostenosis)

– Obstruction of the gastro-intestinal tract, ileus, inflammatory colonic ulcers

– Intestinal atony

– Severe dilatation of the colon (toxic megacolon)

– Myasthenia gravis

Oxybutynin STADA 5 mg contains lactose, therefore they should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Use in children
Oxybutynin STADA 5 mg is not intended for use in children under 5 years of age.

4.4 Special warnings and precautions for use

Caution should be exercised in elderly patients and children because these may show a more sensitive response to oxybutynin. Elderly patients and children, therefore, may require lower dosages.

Caution should be exercised in patients with autonomic neuropathy, hiatus hernia with gastrooesophageal reflux disease or any other severe disorder of the gastro-intestinal tract.

Caution should also be exercised in patients with hepatic and/or renal impairment, especially in those with severe impairment, as no pharmacokinetic data are available on these patient groups. Dosage reduction may be necessary.

Oxybutynin hydrochloride may exacerbate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy.

Caution should be exercised in patients with fever or when oxybutynin hydrochloride is administered in the presence of high environmental temperature because decreased sweating (a side effect of oxybutynin hydrochloride) may result in heat stroke.

Chronic use may result in the development of dental caries, periodontal disease, thrush and discomfort as a consequence of reduction or inhibition of salivation.

Urogenital tract infection occurring during Oxybutynin STADA 5 mg therapy requires institution of appropriate antibacterial therapy.
Safe use of oxybutynin hydrochloride in children under 5 years of age has not been established.

As Oxybutynin STADA 5 mg may trigger angle-closure glaucoma, visual acuity and intraocular pressure should be monitored periodically during therapy.

Oxybutynin hydrochloride tablets should not be used to treat stress or stress urinary incontinence.

Caution should be exercised in patients with frequency of micturition or nocturia due to cardiac or renal insufficiency.

Patients should be advised to seek advice immediately if they are aware of a sudden loss of visual acuity.

In patients with Parkinson disease and/or pre-existing cognitive impairment, oxybutynin may trigger neuropsychiatric side effects.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken if other anticholinergic agents are used together with oxybutynin, as potentiation of anticholinergic effects may occur. The anticholinergic activity of oxybutynin is increased by concurrent use of other anticholinergics or drugs with anticholinergic activity, such as:

– amantadine and other antiparkinsonian drugs (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones)

– quinidine

– tricyclic antidepressants

– atropine and related compounds.

By reducing gastro-intestinal motility, oxybutynin may alter the absorption of other drugs.

As oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4, interactions with drugs that inhibit this isoenzyme cannot be ruled out. This should be borne in mind when using azole antifungals (e.g. ketoconazole) or macrolide antibiotics (e.g. erythromycin) concurrently with oxybutynin. Itraconazole has been demonstrated to inhibit oxybutynin metabolism. This led to the doubling of the oxybutynin plasma levels, but only to a 10% increase for the active metabolite. Because the metabolite is responsible for about 90% of the antimuscarinic activity, the changes appear to be of minor clinical significance.

The effects of prokinetics (e.g. cisapride, metoclopramide, domperidone) on gastro-intestinal motility may be decreased by the concomitant treatment with oxybutynin.

4.6 Pregnancy and lactation

There is no clinical practice experience with use of oxybutynin in pregnant women. Animal studies during the reproduction process revealed toxic effects on the offspring (cf. section 5.3).

Therefore, oxybutynin must not be used in the first trimester of pregnancy and should be used in the second and third trimesters only if clearly needed. As oxybutynin is excreted in breast milk, it must not be used during lactation.

4.7 Effects on ability to drive and use machines

Even when used as directed, this medicinal product may alter reaction times and visual acuity to such an extent that the ability to actively participate in road traffic, operate machines or work without a firm support is impaired, especially at the start of therapy, when increasing the dose, switching medications or using alcohol at the same time.

4.8 Undesirable effects

The side-effects of oxybutynin are mainly due to its anticholinergic activity. Dose reduction may reduce the incidence of these side-effects.

Side effects	Very common (> 1/10)	Common (>1/100; <1/10)	Uncommon (>1/1000, <1/100)	Rare (>1/10000, <1/1000)	Very rare (including isolated reports) (< 1/10000)
Gastrointestinal disorders	dry mouth	constipation, nausea, abdominal discomfort dyspepsia	diarrhea, vomiting, anorexia	heart burn, reflux esophagitis	
Psychiatric disorders			hallucinations, confusion, disorientation, agitation, anxiety, passivity	concentration and behavioral disorders, paranoia	nightmares
CNS disorders		vertigo, dizziness	headache, fatigue		convulsions
Eye and vision disorders		blurred vision, mydriasis	dry eyes		glaucoma
Cardiac disorders			tachycardia	palpitation, arrhythmia	
Skin and subcutaneous tissue disorders		skin redness, facial flushing	dry skin		angioedema, allergic skin reactions (erythema, urticaria), photosensitisation
Renal, urinary and Reproductive system disorders		problems with micturition		urinary retention	impotence
General disorders					heat stroke

4.9 Overdose

Symptoms of poisoning
Overdosage with Oxybutynin STADA 5 mg is characterised by increased anticholinergic (side) effects. Patients may experience symptoms of (exaggerated) responses of the central nervous system (e.g. ataxia, confusion, nervous restlessness, excitement, hallucinations to the point of psychotic behaviour) and circulatory system (e.g. flushing, tachycardia and dizziness), as well as dilatation of the pupils (mydriasis), fever, hot, red skin, dry mucous membranes, respiratory failure, paralysis and coma.

Management of poisoning
In the event of overdose, and if possible, immediate gastric lavage should be performed and activated charcoal to prevent absorption should be given.

Adult dosage:
Give 0.5–2mg of physostigmine by slow intravenous administration. Repeat after 5 minutes if necessary up to a maximum total dose of 5mg.

Paediatric dosage:
Give 30µg/kg of physostigmine by slow intravenous administration. Repeat after 5 minutes if necessary up to a maximum total dose of 2mg.

Diazepam 10mg i.v. may be injected in case of pronounced nervous restlessness or agitation. Tachycardia can be treated with intravenous propranolol, and urinary retention can be managed by catheterisation of the urinary bladder. Should the muscle relaxant effect progress to respiratory paralysis, mechanical ventilation is indicated.
Fever should be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code
G04B D04

Pharmacotherapeutic group
Anticholinergic and spasmolytic

Oxybutynin hydrochloride (4-diethylamino-2-butynyl-2-phenyl-2-cyclohexylglycolate hydrochloride) – a synthetic tertiary amine – is an anticholinergic agent with additional antispasmodic activity on bladder smooth muscle. Oxybutynin exhibits about one fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle.

Oxybutynin increases bladder capacity, reduces the frequency of uninhibited contractions of the detrusor muscle and delays the initial desire to void. Oxybutynin thus relieves the symptoms of bladder instability (urinary incontinence).

5.2 Pharmacokinetic properties

Oxybutynin is absorbed rapidly, attaining peak plasma concentrations after 30–90 minutes. Large inter-individual variations in plasma concentrations are seen. Concurrent ingestion of food, especially of a meal rich in fat, delays oxybutynin absorption, but increases overall bioavailability.

The duration of action of oxybutynin hydrochloride is 6–10 hours. Oxybutynin is subject to extensive first pass metabolism. Oxybutynin hydrochloride is metabolised via cytochrome P 3A4. Differences in individual predisposition may result in significant interindividual variations in oxybutynin metabolism.

The bioavailability of oral oxybutynin hydrochloride is 2–11%. Main metabolites are inactive metabolite 2,2-phenylcyclohexylglycolic acid and active metabolite *N*-desethyloxybutynin, which has similar pharmacological activity to oxybutynin.
Oxybutynin elimination is biphasic. *N*-Desethyloxybutynin elimination is monophasic. Mean elimination half life is 2 hours. In elderly patients, especially the frail elderly, the bioavailability (2-4 times higher AUC after multiple dosing) and half-life (3-5 hours) are increased. Urinary excretion has been established as less than 0.02% of an administered dose. Oxybutynin is 83-85% plasma albumin bound.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of general toxicity, genotoxicity and carcinogenicity beyond the information included in other sections of the SPC.

Embryofetal studies in pregnant rats showed malformed hearts. Higher dosages additionally were associated with extra thoracolumbar ribs and increased neonatal mortality. Reproductive toxicity occurred only with concurrent general maternal toxicity. In the absence of exposure data, the relevance of these observations cannot be assessed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose powdered, lactose monohydrate, magnesium stearate, talc

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

PVC/aluminium foil blister strip

Original packs of 10, 20, 28, 30, 50, 56, 60, 90, 100, 250, 300, 500 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastrasse 2-18
D-61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/22/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th November 2000
Date of last renewal: 4th September 2003

10 DATE OF REVISION OF THE TEXT

February 2007