

SUMMARY OF PRODUCT CHARACTERISTICS**1. NAME OF THE MEDICINAL PRODUCT**

Oxybutynin Hydrochloride Tablets 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxybutynin hydrochloride 5mg

Excipient(s) with known effect: Contains 153.00 mg Lactose monohydrate per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Blue, round, biconvex, uncoated tablets, marked OB score-line 5 on one side and plain on the reverse

4. CLINICAL PARTICULARS**4.1 Therapeutic indications***Adults*

Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic detrusor instability (motor urge incontinence) or neurogenic bladder disorders (detrusor hyperreflexia) in conditions such as multiple sclerosis and spina bifida.

Paediatric population

Oxybutynin hydrochloride is indicated in children over 5 years of age for:

- Urinary incontinence, urgency and frequency in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor over activity)
- Nocturnal enuresis associated with detrusor over activity, in conjunction with non-drug therapy, when other treatment has failed

4.2 Posology and method of administration*Adults*

The usual initial dose is 5mg two or three times a day. This dose may be increased to a maximum dose of 5mg four times a day to obtain a clinical response provided that the side effects are well-tolerated.

Elderly (including frail elderly)

A lower dose is recommended because the elimination half-life is increased in the elderly. A dose of 2.5mg twice a day is likely to be adequate, particularly if the patient is frail. This dose may be increased if necessary to 5mg twice a day provided that the side effects are well tolerated.

Children (under 5 years of age)

Not recommended

Children (over 5 years of age)

Neurogenic bladder instability: The usual dose is 2.5mg twice a day. This dose may be increased, if necessary, to 5mg two or three times daily provided that the side effects are well-tolerated.

Nocturnal enuresis: The usual dose is 2.5mg twice a day. This dose may be increased, if necessary, to 5mg two or three times daily provided that the side effects are well-tolerated. The last dose should be given before bedtime.

4.3 Contraindications

Oxybutynin hydrochloride tablets are contraindicated in patients with:

- hypersensitivity to oxybutynin hydrochloride or any of the excipients listed in section 6.1.
- myasthenia gravis
- narrow-angle glaucoma or shallow anterior chamber.
- gastrointestinal obstruction including pyloric stenosis, paralytic ileus and intestinal atony.
- ileostomy, colostomy, toxic megacolon, severe ulcerative colitis.
- bladder flow obstruction where urinary retention may be precipitated.
- porphyria
- frequent urination at night caused by heart or kidney disease

4.4 Special warnings and precautions for use

Oxybutynin hydrochloride tablets should be used with caution in the frail elderly and children who may be more sensitive to the effects of the product and in patients with autonomic neuropathy (such as those with Parkinson's disease), severe gastrointestinal motility disorders, hepatic or renal impairment (also see section 4.3).

Anticholinergics should be used with caution in elderly patients due to the risk of cognitive impairment.

Gastrointestinal disorders: Anticholinergic medicinal products may decrease gastrointestinal motility and should be used with caution in patients with gastrointestinal obstructive disorders, intestinal atony and ulcerative colitis.

Oxybutynin may aggravate tachycardia (and thus be cautious in case of hyperthyroidism, congestive heart failure, cardiac arrhythmia, coronary heart disease, hypertension), cognitive disorders and symptoms of prostatic hypertrophy.

Anticholinergic central nervous system (CNS) effects (e.g. hallucinations, agitation, confusion, somnolence) have been reported; monitoring recommended especially in first few months after initiating therapy or increasing the dose; consider discontinuing therapy or reducing the dose if anticholinergic CNS effects develop.

Since oxybutynin can cause narrow-angle glaucoma, patients should be advised to contact a physician immediately if they are aware of a sudden loss of visual acuity or ocular pain.

Oxybutynin may reduce salivary secretions which could result in dental caries, parodontosis or oral candidiasis. Regular dental check-ups are therefore advisable during long-term treatment.

Anticholinergic medicinal products should be used with caution in patients who have hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.

When oxybutynin is used in high environmental temperatures, this can cause heat prostration due to decreased sweating.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Paediatric population

The use of oxybutynin in children under 5 years of age is not recommended; it has not been established whether oxybutynin can be safely used in this age group.

There is limited evidence supporting the use of oxybutynin in children with monosymptomatic nocturnal enuresis (not related to detrusor over activity).

In children over 5 years of age, oxybutynin hydrochloride should be used with caution as they may be more sensitive to the effects of the product, particularly the CNS and psychiatric adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken if other anticholinergic agents are administered together with oxybutynin, as potentiation of anticholinergic effects may occur.

The anticholinergic activity of oxybutynin is increased by concurrent use of other anticholinergics or medicinal products with anticholinergic activity, such as amantadine and other anticholinergic anti-Parkinsonian medicinal products (e.g. biperiden, levodopa), antihistamines, antipsychotics (e.g. phenothiazines, butyrophenones, clozapine), quinidine, digitalis, tricyclic antidepressants, atropine and related compounds like atropinic antispasmodics and dipyrindamole.

By reducing gastric motility, oxybutynin may affect the absorption of other drugs. Oxybutynin is metabolised by cytochrome P 450 isoenzyme CYP 3A4. Concomitant administration with a CYP3A4 inhibitor can inhibit oxybutynin metabolism and increase oxybutynin exposure (e.g. ketoconazole, itraconazole, erythromycin). Oxybutynin may antagonise prokinetic therapies (e.g. metoclopramide and domperidone).

Concomitant use with cholinesterase inhibitors may result in reduced cholinesterase inhibitor efficacy.

Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin (see section 4.7).

4.6 Fertility, pregnancy and lactation**Pregnancy:**

There are no adequate data from the use of oxybutynin in pregnant women. Studies in animals have shown minor reproductive toxicity (see section 5.3). Animal studies are insufficient with respect to effects on pregnancy, embryonic / foetal development, parturition or postnatal development (see section 5.3). The potential risk for humans is unknown. Oxybutynin should not be used in pregnancy unless clearly necessary.

Breast-feeding:

Oxybutynin in small amount is excreted in breast milk during lactation. Oxybutynin should not be used during breast-feeding.

Fertility:

There are no data regarding effects on human fertility. Studies in animals have shown impaired fertility in females.

4.7 Effects on ability to drive and use machines

Oxybutynin hydrochloride tablets can cause drowsiness or blurred vision and patients should be cautioned regarding activities requiring mental alertness such as driving, operating machinery or performing hazardous work.

4.8 Undesirable effects

Classification of expected frequencies:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); not known (cannot be estimated from the available data).

The following adverse events (marked with an asterisk *), which has not been observed in clinical trials but reported after the drug has been marketed, has been ranked in the frequency of "rare/unknown".

	Very Common	Common	Uncommon	Rare	Not Known
Infections and infestations					urinary tract infection
Immune System Disorders					hypersensitivity
Psychiatric disorders		confusional state		restlessness, disorientation, concentration difficulties	excitation, anxiety*, hallucinations, nightmares*, paranoia, agitation, cognitive disorders in elderly, symptoms of depression, dependence to oxybutynin (in

					patients with history of drug or substance abuse)
Nervous System Disorders	somnolence, fatigue, headache, dizziness		drowsiness		Cognitive disorders*, convulsions*, disorientation
Eye disorders	decreased tear production /dry eyes, vision blurred		light hypersensitivity		Narrow angle closure glaucoma*, mydriasis, ocular hypertension
Cardiac disorders					cardiac arrhythmias, tachycardia
Vascular disorders	flushing which may be more marked in children				
Gastrointestinal Disorders	dry mouth, nausea, constipation	diarrhoea, vomiting, dyspepsia	anorexia, dysphagia, abdominal discomfort/pain, decreased appetite		gastroesophageal reflux disease, pseudo-obstruction in patients at risk (elderly or patients with constipation and treated with other drugs that decrease intestinal motility)
Skin and subcutaneous tissue disorders	dry skin/ decreased sweating			phototoxicity	angioedema, rash, urticaria, hypohidrosis,
Renal and urinary disorders	urinary retention				difficulty in micturition
Reproductive system and breast disorders				erectile dysfunction	
Injury, poisoning and procedural complications					heat stroke

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The symptoms of over dosage with oxybutynin progress from an intensification of the usual side effects of CNS disturbances (from restlessness and excitement to psychotic behaviour), circulatory changes (flushing, fall in blood pressure, circulatory failure etc.), respiratory failure, paralysis and coma.

Measures to be taken are:

1. Immediate gastric lavage
2. Physostigmine by slow intravenous injection

Adults: 0.5 to 2.0 mg of physostigmine by slow intravenous administration. Repeat after 5 minutes, if necessary up to a maximum total dose of 5mg.

Children: 30 micrograms/kg of physostigmine by slow intravenous administration. Repeat after 5 minutes, if necessary up to a maximum total dose of 2mg.

Fever should be treated symptomatically with tepid sponging or ice packs.

In pronounced restlessness or excitation, diazepam 10mg may be given by intravenous injection, tachycardia may be treated by intravenous injection of propranolol and urinary retention can be managed by bladder catheterisation.

In the event of progression of the curare-like effect to the paralysis of the respiratory muscles, mechanical ventilation will be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04BD04

Oxybutynin has a direct antispasmodic effect on the smooth muscle of the bladder detrusor. Oxybutynin also inhibits the effects of acetylcholine on smooth muscle by blocking muscarinic receptors. Pharmacological models have established differences in affinity for subtypes of muscarinic receptors.

The pharmacodynamic properties of oxybutynin result in relaxation of the bladder detrusor muscle. Patients with unstable bladder experience increased bladder volume and a decreased incidence of spontaneous contractions of the detrusor muscle.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, oxybutynin is rapidly absorbed from the gastrointestinal tract (t_{max} 0.5-1.4hours). Studies have established a C_{max} after a 5-10mg dose in young healthy

patients of 8-12ng/ml. Larger inter-individual variations in plasma concentrations are seen. Oxybutynin is subject to extensive first pass metabolism, resulting in an absolute systemic availability of 6.2%.

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 L after intravenous administration of 5 mg oxybutynin hydrochloride.

Biotransformation

Oxybutynin is extensively metabolised by the liver, primarily by the cytochrome P450 enzyme system, particularly CYP 3A4 found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and N-desethyloxybutynin, which is pharmacologically active.

Elimination

Oxybutynin undergoes extensive hepatic metabolism, with less than 0.02% of the administered dose excreted unchanged in the urine. Less than 0.1% of the administered dose is excreted as the metabolite N-desethyloxybutynin.

Oxybutynin is 83-85% plasma albumin bound.

Oxybutynin is eliminated biexponentially. Mean elimination half-life is 2 hours. Repeated administration results in little accumulation.

Elderly

Bioavailability is higher in elderly patients; AUC is 2-4-fold higher after repeated administration and half-life 3-5 times longer.

5.3 Preclinical safety data

Oxybutynin hydrochloride has been shown to have low acute toxicity when administered orally to either mice, rats or dogs. In a repeat dosing experiment of 6 months duration in rats, daily oral doses of 63mg/kg or more were associated with decreases in food consumption and body weight gain and with minor pathological changes in the liver and kidneys. At daily oral doses of 6mg/kg administered for 6 months, dogs exhibited transient anorexia, tremors and nervousness but these effects were not associated with microscopic signs of tissue damage.

There is no evidence from preclinical studies to suggest either mutagenic or carcinogenic activity for oxybutynin.

Reproduction tests indicate no adverse effects on fertility or reproductive performance in rats given daily oral doses of 15mg/kg. Oxybutynin hydrochloride was not teratogenic in rats and rabbits at oral dose levels (20mg/kg/day in rats and 48mg/kg/day in rabbits) which did not cause significant maternal toxicity. At maternally toxic doses of oxybutynin (100mg/kg/day), increased incidence of extra thoracolumbar ribs in rat foetuses, as well as mortality of neonates, was observed. At oral daily dose levels up to 20mg/kg in rats, oxybutynin hydrochloride had no adverse effects on gestation or on the birth and development of offspring up to weaning.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Calcium stearate
Indigo carmine (aluminium lake) E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C in a dry place. Protect from light.

6.5 Nature and contents of container

Polypropylene tablet container with tamper-evident polyethylene cap
Pack sizes: 20, 30, 50, 60, 84, 90, 100, 250, 500

PVC (250µm ± 5µm)/aluminium foil (20µm) blister packs
Pack sizes: 20, 30, 50, 56, 60, 84, 90, 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No specific instructions for use/handling

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd.
Unit 4, Metro Centre,
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Watford, Hertfordshire
WD18 9SS
Trading as: Co-pharma

8. MARKETING AUTHORISATION NUMBER(S)

PL 13606/0071

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 June 1998 / 21 March 2006

10. DATE OF REVISION OF THE TEXT

17/08/2018