SUMMARY OF PRODUCT CHARACTERISTICS OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS USP 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Oxybutynin Chloride USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Extended release tablet contains

Oxybutynin chloride USP……5mg

3. PHARMACEUTICAL FORM

Oxybutynin Chloride extended-release tablets are available as 5 and 10 mg tablets for oral use.

Physical Appearance of Tablet: "Pale yellow coloured, round, biconvex tablets with orifice".

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oxybutynin chloride is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Oxybutynin chloride is also indicated for the treatment of pediatric patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida).

4.2. Posology and method of administration

Oxybutynin chloride must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

Adults

The recommended starting dose of Oxybutynin chloride is 5 or 10 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Pediatric Patients Aged 6 Years of Age and Older

The recommended starting dose of Oxybutynin chloride is 5 mg once daily at approximately the same time each day. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

4.3. Contraindications

Oxybutynin chloride is contraindicated in patients with urinary retention, gastric retention and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma.

Oxybutynin chloride is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product. There have been reports of hypersensitivity reactions, including anaphylaxis and angioedema.

4.4. Special warnings and precautions for use Angioedema

Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin. In some cases, angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, oxybutynin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Central Nervous System Effects

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how Oxybutynin chloride affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Oxybutynin chloride should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.
Oxybutynin chloride should be used with caution in patients with Parkinson's disease due to the risk of aggravation of symptoms.

Worsening of Symptoms of Myasthenia Gravis

Oxybutynin chloride should be used with caution in patients with myasthenia gravis due to the risk of aggravation of symptoms.

Worsening of Symptoms of Decreased Gastrointestinal Motility in Patients with Autonomic Neuropathy

Oxybutynin chloride should be used with caution in patients with autonomic neuropathy due to the risk of aggravation of symptoms of decreased gastrointestinal motility.

Urinary Retention

Oxybutynin chloride should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Gastrointestinal Adverse Reactions

Oxybutynin chloride should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention.
Oxybutynin chloride, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.
Oxybutynin chloride should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.
As with any other nondeformable material, caution should be used when administering Oxybutynin chloride to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in

patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

4.5. Interaction with other medicinal products and other forms of interaction

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents which produce dry mouth, constipation, somnolence (drowsiness), and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects.

Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. This may be of concern for drugs with a narrow therapeutic index. Anticholinergic agents may also antagonize the effects of prokinetic agents, such as metoclopramide.

Mean oxybutynin plasma concentrations were approximately 2 fold higher when Oxybutynin chloride was administered with ketoconazole, a potent CYP3A4 inhibitor. Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., Cmax and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

4.6. Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category B. There are no adequate and well-controlled studies using Oxybutynin chloride in pregnant women. Oxybutynin chloride should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during Oxybutynin chloride treatment are encouraged to contact their physician.

Risk Summary

Based on animal data, oxybutynin is predicted to have a low probability of increasing the risk of adverse developmental effects above background risk.

Animal Data

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no evidence of impaired fertility or harm to the animal fetus.

Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Oxybutynin chloride is administered to a nursing woman.

Pediatric Use

The safety and efficacy of Oxybutynin chloride were studied in 60 children in a 24-week, open-label, non-randomized trial. Patients were aged 6-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that administration of Oxybutynin chloride 5 to 20 mg/day was associated with an increase from baseline in mean urine volume per catheterization from 108 mL to 136 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 189 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 51%.

Urodynamic results were consistent with clinical results. Administration of Oxybutynin chloride resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H_2O to 33 cm H_2O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_2O) from 60% to 28%.

The pharmacokinetics of Oxybutynin chloride in these patients were consistent with those reported for adults.

Oxybutynin chloride is not recommended in pediatric patients who cannot swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6.

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar. The pharmacokinetics of Oxybutynin chloride were similar in all patients studied (up to 78 years of age).

Renal Impairment

There were no studies conducted with Oxybutynin chloride in patients with renal impairment.

Hepatic Impairment

There were no studies conducted with Oxybutynin chloride in patients with hepatic impairment.

4.7. Effects on ability to drive and use machines

Oxybutynin has minor influence on the ability to drive and use machines. Oxybutynin may produce drowsiness or blurred vision; therefore, patients should be cautioned regarding activities requiring mental alertness such as driving, operating machinery or performing hazardous work while taking this drug

4.8. Undesirable effects

Infections and Infestations: Urinary tract infection;

Psychiatric Disorders: psychotic disorder, agitation, confusional state, hallucinations, memory impairment, abnormal behavior, insomnia;

Nervous System Disorders: convulsions, headache, somnolence, dizziness, dysgeusia;

Eye Disorders: glaucoma, vision blurred, dry eye;

Respiratory, Thoracic and Mediastinal Disorders: nasal congestion, cough, oropharyngeal pain, dry throat, nasal dryness, dysphonia;

Gastrointestinal Disorders: Dry mouth, constipation, diarrhoea, dyspepsia, nausea, abdominal pain, vomiting, flatulence, gastro-esophageal reflux disease, dysphagia, frequent bowel movements;

Cardiac Disorders: arrhythmia, tachycardia, palpitations, QT interval prolongation;

Vascular Disorders: flushing, hypertension;

Skin and Subcutaneous Tissue Disorders: rash, dry skin, pruritis;

Renal and Urinary Disorders: impotence, dysuria, urinary hesitation, urinary retention;

General Disorders and Administration Site Conditions: Fatigue, hypersensitivity reactions, including angioedema with airway obstruction, urticaria, and face edema, chest discomfort, thirst, anaphylactic reactions requiring hospitalization for emergency treatment;

Metabolism and Nutrition Disorders: anorexia, fluid retention;

Investigations: Residual urine volume;

Injury, poisoning and procedural complications: fall.

Additional adverse events reported with some other oxybutynin chloride formulations include: cycloplegia, mydriasis, and suppression of lactation.

In one reported case, concomitant use of oxybutynin with carbamazepine and dantrolene was associated with adverse events of vomiting, drowsiness, confusion, unsteadiness, slurred speech and nystagmus, suggestive of carbamazepine toxicity.

4.9. Overdose

The continuous release of oxybutynin from Oxybutynin chloride should be considered in the treatment of over dosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. A cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

Ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients fully recovered with symptomatic treatment.

5. PHARMACOLOGICAL PROPERTIES

Mechanism of Action

Oxybutynin relaxes bladder smooth muscle. Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antinicotinic effects).

Antimuscarinic activity resides predominantly in the R-isomer. A metabolite, desethyloxybutynin, has pharmacological activity similar to that of oxybutynin in in vitro studies.

5.1. Pharmacodynamics properties

In patients with conditions characterized by involuntary bladder contractions, cystometric studies have demonstrated that oxybutynin increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void.

5.2. Pharmacokinetic properties

Absorption

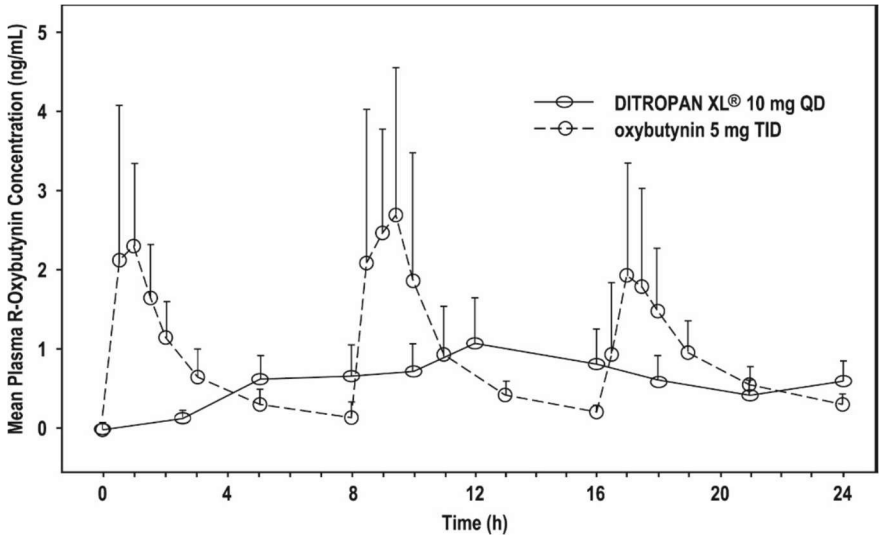
Following the first dose of Oxybutynin chloride, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bio availabilities of R-and S-oxybutynin from Oxybutynin chloride are 156% and 187%, respectively, compared with oxybutynin. The mean pharmacokinetic parameters for R-and S-oxybutynin are summarized in Table 2. The plasma concentration-time profiles for R-and S-oxybutynin are similar in shape; Figure 1 shows the profile for R-oxybutynin.

Table 2: Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters Following a Single Dose of Oxybutynin chloride 10mg (n=43)

Parameters (units)	R-Oxybutynin		S-Oxybutynin	
Cmax (ng/mL)	1.0	(0.6)	1.8	(1.0)
Tmax (h)	12.7	(5.4)	11.8	(5.3)
t1/2 (h)	13.2	(6.2)	12.4	(6.1)
AUC(0-48) (ng·h.mL)	18.4	(10.3)	34.2	(16.9)
AUCinf (ng·h/mL)	21.3	(12.2)	39.5	(21.2)

Figure 1: Mean R-oxybutynin plasma concentrations following a single dose of Oxybutynin chloride 10mg and oxybutynin 5mg administered every 8 hours (n=23 for each treatment)



Steady state oxybutynin plasma concentrations are achieved by Day 3 of repeated Oxybutynin chloride dosing, with no observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

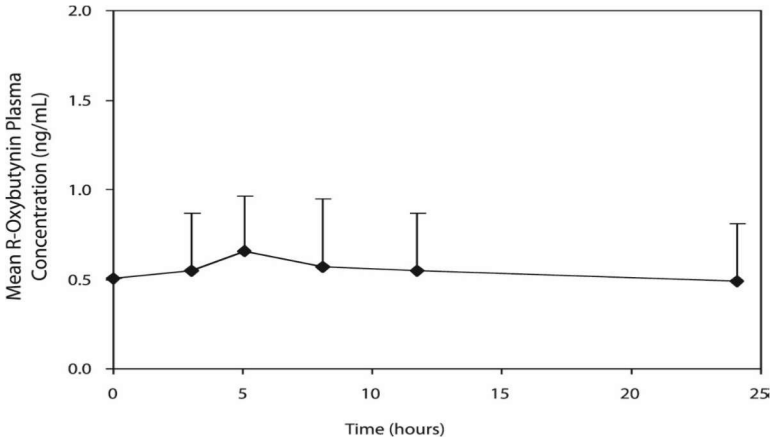
Oxybutynin chloride steady state pharmacokinetics were studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina

bifida). The children were on Oxybutynin chloride total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5 mg per day of Oxybutynin chloride, the mean pharmacokinetic parameters derived for R-and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 3. The plasma-time concentration profiles for R-and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 3: Mean ± SD R- and S-Oxybutynin and R- and S-Desethyl-oxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20 mg Oxybutynin Chloride Once Daily (n=19), All Available Data Normalized to an Equivalent of Oxybutynin chloride 5 mg

	R-Oxybutynin	**S-Oxybutynin**	**R-Desethyloxybutynin**	**S-Desethyloxybutynin**
C_{max} (ng/mL)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T_{max} (h)	5.0	5.0	5.0	5.0
AUC (ng•h/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

Figure 2: Mean steady state (± SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Oxybutynin chloride once daily in children aged 5-15. Plot represents all available data normalized to an equivalent of Oxybutynin chloride 5 mg once daily.



Food Effects

The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Distribution

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride. Both enantiomers of oxybutynin are highly bound (>99%) to plasma proteins. Both enantiomers of N-desethyloxybutynin are also highly bound (>97%) to plasma proteins. The major binding protein is alpha-1 acid glycoprotein.

Metabolism

Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4 found mostly in the liver and gut wall. Its metabolic products include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and desethyloxybutynin, which is pharmacologically active. Following Oxybutynin chloride administration, plasma concentrations of R-and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine. Also, less than 0.1% of the administered dose is excreted as the metabolite desethyloxybutynin.

Dose Proportionality

Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of 5-20 mg of Oxybutynin chloride are dose proportional.

Use in Specific Populations

Pediatric

The pharmacokinetics of Oxybutynin chloride were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of Oxybutynin chloride in these pediatric patients were consistent with those reported for adults.

Gender

There are no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following administration of Oxybutynin chloride.

Race

Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of Oxybutynin chloride.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum human exposure, based on a human equivalent dose taking into account normalization of body surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae, and Salmonella typhimurium test systems.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no evidence of impaired fertility.

6. PHARMACEUTICAL PARTICULARS

6.1.List of excipients

Polyethylene Oxide (Polyox WSR N80 FP) NF,
Hypromellose (Methocel premium E3LV) USP
Sodium Chloride USP
Ferric oxide (SICOVIT YELLOW 10E172) NF
Butylated Hydroxyl toluene NF
Isopropyl Alcohol USP
Methyl Alcohol NF Colloidal
silicon dioxide NF
Magnesium Stearate NF
Polyethylene Oxide (Polyox WSR 303) NF
Ferric Oxide (Black) (Koelin PH-999) NF
Cellulose Acetate (CA-398-10) NF
Polyethylene Glycol 3350 NF
Acetone NF
Methyl Alcohol NF
Opadry II Yellow 33G520007IH
Purified Water USP

6.2.Incompatibilities

6.3.Shelf life

24 Months

6.4.Special precautions for storage

Store below 30°C. in a dry place. Protect from light.

6.5.Nature and contents of container

Alu-PVC Blister of 10 Tablets. 10 such blisters are packed in a carton along with leaflet.

7. MARKETING AUTHORISATION HOLDER

Unique Pharmaceutical Laboratories
(A Division of J.B. Chemicals & Pharmaceuticals Ltd)

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0196

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

04th May, 2022

10. DATE OF REVISION OF THE TEXT