PRODUCT MONOGRAPH

Pr**UROMAX®**

Oxybutynin Chloride

Controlled Release Tablets – 5, 10 and 15 mg

Anticholinergic-Antispasmodic
ATC: G04BD04

Purdue Pharma
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Pickering, ON
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Oxybutynin Chloride
Controlled Release Tablets - 5, 10 and 15 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Controlled release tablets 5, 10 mg and 15 mg	None *For a complete listing of other ingredients see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Uromax® (oxybutynin chloride controlled release tablets) is indicated for:
- treatment of patients with symptoms of an overactive bladder including urge incontinence, urinary frequency, urgency or any combination of these symptoms.

Geriatrics:
Available data (see clinical trials section) does not suggest a difference in the balance between efficacy and adverse event profile in patients over the age of 65 years and less than 65 years.

Pediatrics:
No data is available on use in children.

CONTRAINDICATIONS
- Patients who are hypersensitive to oxybutynin or to any ingredient in the formulation (for a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section).
- Partial or complete obstruction of the gastrointestinal tract
- Paralytic ileus
- Intestinal atony of the elderly or debilitated patient
- Megacolon
- Toxic megacolon complicating ulcerative colitis
- Glaucoma
- Myasthenia gravis
- Obstructive uropathy
- Unstable cardiovascular status in acute haemorrhage

WARNINGS AND PRECAUTIONS

General
When oxybutynin is administered in the presence of high environmental temperature, it can cause heat prostration (fever and heat stroke due to decreased sweating).

Oxybutynin may produce drowsiness or blurred vision. Patients should be cautioned regarding activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug, until it is clear that their ability to do so is not impaired. Alcohol or other sedative drugs may enhance the drowsiness caused by oxybutynin.

Carcinogenesis and Mutagenesis
See animal data in Toxicology section.

Cardiovascular
The symptoms of coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia and hypertension may be aggravated following administration of **Uromax**.

Caution should be used when prescribing antimuscarinimics/anticholinergics to patients with pre-existing cardiac diseases.

Although not reported for immediate-release or controlled-release oxybutynin formulations, newer antimuscarinic agents used in the treatment of urinary incontinence have been reported to prolong the QT/QTc interval of the electrocardiogram. Some drugs that cause QT/QTc prolongation may increase the risk of the rare, but serious ventricular arrhythmia - torsades de pointes. Patients at risk for QT/QTc prolongation, such as those with clinically relevant heart failure, long QT syndrome, recent significant hypokalemia, or receiving other drugs known to prolong QT/QTc, should be appropriately monitored when receiving oxybutynin. Patients who develop prolonged QT/QTc or symptoms of possible arrhythmia such as dizziness, palpitations, or fainting should be evaluated electrocardiographically and for electrolyte disturbances.

Endocrine and Metabolism
The symptoms of hyperthyroidism may be aggravated following administration of oxybutynin.

Gastrointestinal
Diarrhea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In such cases, treatment with oxybutynin would be inappropriate and possibly harmful.

Administer with caution to patients with hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition.

Administration of oxybutynin in large doses to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

Genitourinary
The symptoms of prostatic hypertrophy may be aggravated following administration of oxybutynin.

Hepatic/Biliary/Pancreatic
Use with caution in patients with hepatic impairment.

Neurologic
Oxybutynin may cause drowsiness.

Use with caution in patients with autonomic neuropathy.

Ophthalmologic
Oxybutynin may produce blurred vision.

Renal
Use with caution in patients with renal impairment.

Special Populations
Pregnant Women: The safety of **Uromax** in pregnancy has not been established. Therefore, it should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

Nursing Women: It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Uromax** is administered to a nursing woman.

Pediatrics (< 18 years of age): Because the safety of **Uromax** tablets in children has not been evaluated, use of the drug in this age group should be with appropriate caution.

Geriatrics: Uromax should be used with caution in debilitated patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The most frequent adverse effects of oxybutynin are those related to its anticholinergic (antimuscarinic) effects, most notably dry mouth and pharyngitis. Although the incidence of dry mouth increased with increasing dose, in **Uromax** clinical trials, patient satisfaction also improved at higher doses because of corresponding improvement in control of urinary incontinence.

Clinical Trial Adverse Drug Reactions
Because clinical trials are conducted under very specific conditions the adverse event rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse event information from

clinical trials is useful for identifying potential drug-related adverse reactions and for approximating their rates.

Table 1 includes spontaneously reported adverse events in three Canadian clinical trials of **Uromax** in patients with urinary incontinence: Study 018-004 was an open-label, sequential, crossover comparison with immediate-release (IR) oxybutynin (12 patients); Study 018-005 was a double-blind, randomized, parallel group comparison with IR oxybutynin (65 patients CR; 60 patients IR); and Study 018-009 was a double-blind, randomized, parallel group comparison of doses of 5, 10, and 15 mg per day (77, 77, and 83 patients respectively). Adverse events that were considered by the clinical investigator to be unrelated to the drug are excluded from this list.

Table 1 - Adverse Event Reports in Uromax Clinical Trials (1%)

	Uromax n=314 (%)	**IR oxybutynin N=72 (%)**
Body as a Whole		
Headache	7.0	18.1
Halitosis	6.4	0.0
Asthenia	4.8	13.9
Abdominal Pain	4.5	9.7
Chest Pain	1.6	1.4
Pain	1.6	1.4
Back Pain	1.3	2.8
Cardiovascular		
Vasodilatation	2.9	5.6
Hypertension	1.3	0.0
Palpitation	1.3	0.0
Syncope	0.3	2.8
Central Nervous System		
Dry Mouth	64.0	72.2
Dizziness	6.4	15.3
Insomnia	4.8	0.0
Somnolence	3.2	9.7
Increased Salivation	1.6	1.4
Sleep Disorder	1.6	0.0
Thinking Abnormal	1.6	0.0
Hypertonia	1.0	0.0
Amnesia	0.0	1.4
Depersonalization	0.0	1.4
Hyperkinesia	0.0	1.4
Hypesthesia	0.0	1.4

Table 1 - Adverse Event Reports in Uromax Clinical Trials (1%)

	Uromax n=314 (%)	IR oxybutynin N=72 (%)
Digestive		
Nausea	6.4	12.5
Constipation	5.1	11.1
Dyspepsia	5.1	11.1
Diarrhea	4.8	1.4
Dysphagia	3.8	11.1
Flatulence	2.2	2.8
Stomatitis	1.3	0.0
Anorexia	1.0	5.6
Gastrointestinal Disorder	1.0	0.0
Glossitis	1.0	4.2
Vomiting	1.0	1.4
Eructation	0.6	2.8
Esophagitis	0.0	1.4
Tongue Discoloration	0.0	1.4
Metabolic and Nutritional		
Peripheral Edema	1.9	6.9
Thirst	1.9	5.6
Musculo-Skeletal		
Tenosynovitis	0.0	1.4
Respiratory		
Pharyngitis	28.7	30.6
Rhinitis	5.7	18.1
Cough Increased	3.2	6.9
Epistaxis	1.9	2.8
Voice Alteration	1.9	1.4
Increased Upper Airway Secretion	0.3	1.4
Sinusitis	0.0	1.4
Skin and Appendages		
Dry Skin	10.2	9.7
Rash	1.3	0.0
Pruritus	1.0	1.4
Skin Discoloration	0.3	2.8
Nail Disorder	0.3	1.4
Special Senses		
Taste Perversion	4.1	9.7
Dry Eyes	2.5	12.5

Table 1 - Adverse Event Reports in Uromax Clinical Trials (1%)

	Uromax n=314 (%)	IR oxybutynin N=72 (%)
Amblyopia	1.9	6.9
Eye Pain	0.3	1.4
Mydriasis	0.3	1.4
Taste Loss	0.0	1.4
Urogenital		
Urinary Retention	4.8	1.4
Urinary Tract Infection	4.5	4.2
Dysuria	1.9	2.8
Urinary Frequency	1.6	0.0
Urination Impaired	1.3	4.2
Urinary Urgency	0.3	1.4
Hematuria	0.0	1.4

During the first two or three days of overactive bladder symptom relief, patients may experience dry mouth, constipation, drowsiness or blurred vision. Provided these symptoms are not intolerable, patients should be encouraged to continue at the same dose for a few days since these symptoms tend to decrease in severity, or even disappear, over time. If excessive dry mouth, constipation, drowsiness or blurred vision persists, the dose should be reduced by 5 mg. If it is necessary to reduce the dose, it may be possible to carefully increase it again after three or four days if the symptoms of overactive bladder are not being well controlled.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Body as a Whole: abdomen enlarged, allergic reaction, face edema, lack of drug effect, malaise

Cardiovascular: migraine, syncope

Central Nervous System: akathisia, anxiety, circumoral paresthesia, confusion, depression, libido decreased, nervousness, paresthesia

Digestive: colitis, eructation, increased appetite, liver function tests abnormal, melena, mouth ulceration, tongue disorder

Metabolic and Nutritional: creatinine increased, generalized edema

Musculo-Skeletal: arthritis, joint disorder

Respiratory: hiccup, increased upper airway secretion, lung disorder

Skin and Appendages: hair disorder, nail disorder, skin discolouration, sweating decreased, urticaria, vesiculobullous rash

Special Senses: abnormal vision, conjunctivitis, eye pain, iritis, mydriasis, tinnitus

Urogenital: cystitis, nocturia, urethral pain, urethritis, urinary urgency

Abnormal Hematologic and Clinical Chemistry Findings

Table 2

# Patients	Parameter	Unit	Value Recorded	Reference Range [Low-High]	Clinically Significant
1	ALT/SGPT	U/L	201	5 - 42	2x upper limit
1	AST/SGOT	U/L	80	10 - 40	2x upper limit

Post-Market Adverse Drug Reactions

Other adverse effects reported with other formulations of oxybutynin are: impotence, increased ocular tension, interference with normal heat regulation, mood changes, suppression of lactation, tachycardia, drug idiosyncrasies that may include dermal manifestations or paralysis of the ciliary muscles of the eye causing blurred vision.

DRUG INTERACTIONS

Overview

Oxybutynin is metabolized through the cytochrome P450 system, specifically the 3A4 enzymes. Inhibitors of these enzymes may alter the pharmacokinetics of **Uromax**. The clinical significance of this is unknown. Alcohol may increase drowsiness.

Drug-Drug Interactions

Interactions with other drugs have not been formally investigated.

Drug-Food Interactions

Interactions with foods have not been formally investigated.

Drug-Herb Interactions

Interactions with herbal products have not been formally investigated.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been formally investigated.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- There is a dose-response relationship for the reduction in episodes of urinary incontinence, with the greatest reduction at a daily dose of **Uromax** 15 mg. This is also the dose associated with the highest level of patient satisfaction, even though anticholinergic side effects also increase with increasing dose.

- Although peak plasma concentrations are lower with **Uromax**, than with immediate-release oxybutynin preparations administered three times daily, at the same total daily dose, it is recommended that the daily dose of **Uromax** not be higher than the maximum recommended daily dose for the immediate-release preparation (20 mg).

Recommended Dose and Dosage Adjustment

The recommended initial dose of **Uromax** is 10-15 mg once a day. The dose may be adjusted upwards or downwards in 5 mg increments according to individual efficacy and tolerability. The 5 mg strength is intended for titration, although some patients may respond adequately to a daily dose of 5 mg. The maximum recommended daily dose is 20 mg.

Uromax is designed to allow once daily dosing. If frequency, urgency or incontinence repeatedly occurs at the end of a dose interval, it is generally an indication for a dosage increase, not more frequent administration.

Dose adjustments should be based on the patient's clinical response. Because of the sustained release properties of **Uromax**, dose adjustments should generally be separated by 48 hours. **Uromax** may be taken with or without food. In debilitated patients or patients with impaired hepatic or renal function, it is advisable to initiate at the lowest dose and to increase carefully according to tolerance and response.

Missed Dose

If a patient forgets to take one or more doses, they should take their next dose at the normal time and in the normal amount.

Administration

Uromax tablets should be swallowed intact with the aid of liquids. The tablets should not be crushed, chewed or divided.

OVERDOSAGE

The symptoms of overdose with oxybutynin may be any of those seen with other anticholinergic agents. Symptoms may include signs of CNS excitation (e.g., restlessness, tremor, irritability, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis and coma.

In the event of overdose or exaggerated response, treatment should be symptomatic and supportive. Induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive, or psychotic state) and maintain respiration. Activated charcoal may be administered as well as magnesium sulfate. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication. Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Oxybutynin chloride is a tertiary amine ester with anticholinergic (antimuscarinic), as well as direct spasmolytic and local anesthetic properties. It depresses spontaneous activity of smooth muscle and inhibits contractions produced by non-cholinergic stimulation. It does not have blocking effects at skeletal neuromuscular junctions or autonomic ganglia (nicotinic effects).

In vitro studies of isolated detrusor muscle or intact bladder preparations from several animal species have demonstrated that oxybutynin competitively antagonizes smooth muscle contraction due to acetylcholine or parasympathetic nerve stimulation. In vitro studies of bladder homogenates demonstrate that oxybutynin binds to muscarinic receptor sites.

Oxybutynin also has a direct inhibitory effect on smooth muscle. In vitro studies using isolated detrusor or intact bladder preparations have demonstrated oxybutynin-induced reductions in spontaneous and non-cholinergically induced contractions of the detrusor, with a potency greater than that of atropine. Oxybutynin also demonstrates local anesthetic effects.

The combination of anticholinergic, spasmolytic and local anesthetic actions make oxybutynin a therapeutically useful agent in the treatment of urinary incontinence.

Pharmacodynamics

In patients with urinary incontinence, urodynamic studies have demonstrated that oxybutynin increases maximal bladder capacity, detrusor compliance, and volume at first bladder contraction and first desire to void, and decreases maximum detrusor pressure. These effects are associated with decreases in urgency, frequency of micturition and incontinence episodes.

In a steady-state pharmacokinetic study, stimulated saliva output over 24 hours, was greater with **Uromax** than immediate-release oxybutynin, and subjective evaluations of dry mouth severity were lower with **Uromax** than immediate-release oxybutynin, indicating less propensity for anticholinergic side effects with **Uromax**.

The pharmacodynamics (anticholinergic effects) of oxybutynin at steady state were assessed by measuring Stimulated Saliva Output (SSO), Dry Mouth Severity and Dry Mouth Symptom Score (DMSS) after administration of each treatment. The mean Stimulated Saliva Output was significantly greater for **Uromax** than IR oxybutynin at each observation time point (0-20 hours; $p \leq 0.05$ and at 24 hours; $p < 0.06$) and as a cumulative amount (28.9 g and 21.6 g; $p = 0.0001$). The mean Dry Mouth Severity was less for **Uromax** than IR oxybutynin at each observation time

point (significantly at hours 8, 10, 12, 14 and 24; $p<0.05$) and as a cumulative measure (51.6 ±32.3 and 57.9 ±31.5; p=0.0816). The Mean DMSS Index for **Uromax** was significantly greater than for IR oxybutynin (0.58 ±0.26 and 0.46 ±0.28; p=0.0064) indicating less frequency and bother of dry mouth symptoms for **Uromax**.

The duration of effect of **Uromax** tablets is 24 hours. Once daily dosing with **Uromax** provides comparable reductions in micturition frequency, urgency and incontinence episodes to immediate-release oxybutynin, given three times per day. **Uromax** produced a significant reduction (62%) in night-time incontinence episodes but immediate-release oxybutynin did not. In a study comparing fixed doses of 5, 10 or 15 mg, the reduction in episodes of urinary incontinence was greatest at a daily dose of 15 mg. This was also the dose associated with the greatest level of overall control of urinary symptoms (urgency, frequency and incontinence) and with the highest rating of patient satisfaction, in consideration of both efficacy and side effects.

Pharmacokinetics

Table 3 - Summary of Uromax Single-Dose Mean Pharmacokinetic Parameters in Healthy Subjects

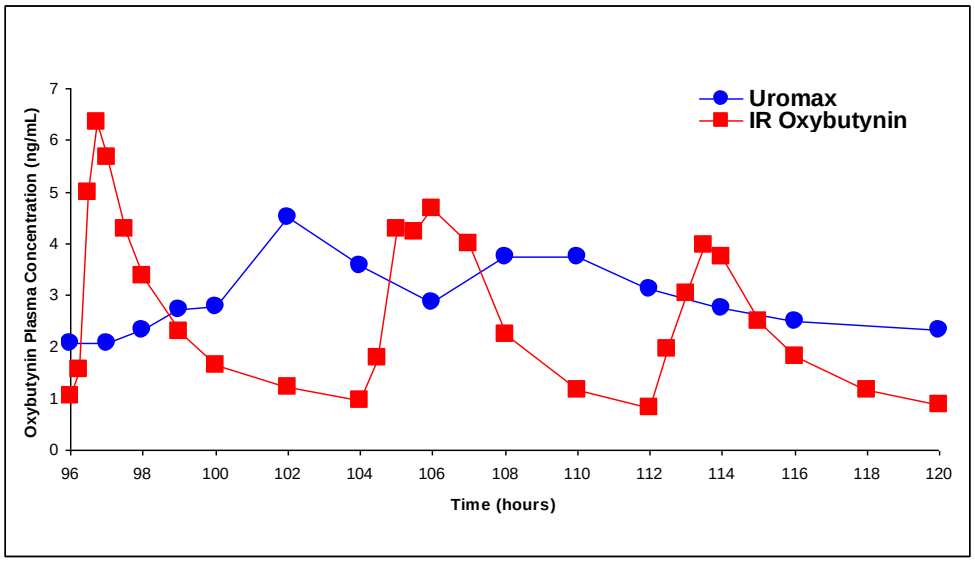
	C_{max} (ng/mL)	T_{max} (h)	AUC_I (ng.hr/mL)
Uromax (fasted)	5.22	11.6	89.22
IR Oxybutynin (fasted)	8.34	0.84	65.42
Uromax (fed)	3.64	10.8	74.54
IR Oxybutynin (fed)	9.87	1.35	81.47

Absorption: Oxybutynin is rapidly absorbed from the gastrointestinal tract when given orally. There is inter-individual variability in absorption and it is increased in the presence of food. The terminal plasma elimination half-life of oxybutynin ranges from 2 to 3 hours in healthy individuals to 5 hours in frail elderly individuals.

The rate of absorption of oxybutynin was lower with **Uromax** than with immediate-release oxybutynin tablets under both fasting and fed conditions, while the extent of absorption of **Uromax** and immediate-release oxybutynin are equivalent under fed and fasted conditions.

At steady-state, the maximum plasma oxybutynin concentration was lower and the minimum concentration higher with **Uromax** (15 mg once daily) than with immediate-release oxybutynin (5 mg q8h) (Relative Cmax 75%; Relative Cmin 220%). Fluctuation in plasma oxybutynin concentrations was lower with **Uromax** than with immediate-release oxybutynin (135% vs. 319%). Extent of absorption was higher with **Uromax** than with immediate-release oxybutynin (Relative AUC 136%) but concentrations of the metabolite N-desethyloxybutynin were lower (Relative AUC 76%; Relative Cmax 54%) and fluctuation was less with **Uromax** than immediate-release oxybutynin (148% vs. 255%) (see Figure 1).

Figure 1: Oxybutynin Plasma Concentration vs. Time



Distribution: Plasma concentrations of oxybutynin decline biexponentially following intravenous or oral administration. The volume of distribution is 193 L after intravenous administration of 5 mg oxybutynin chloride.

Metabolism: Oxybutynin is metabolized through the cytochrome P450 system, specifically the 3A4 enzymes. Oxybutynin is extensively metabolized in the liver and gut wall. The parent compound and the metabolite (N-desethyloxybutynin) are both active and are equipotent. The most abundant but inactive metabolite is phenylcyclohexylglycolic acid.

Excretion: Only negligible amounts of the parent compound are excreted renally.

STORAGE AND STABILITY

Temperature:
Store at room temperature (15-30°C).

Light:
Protect from exposure to light.

Moisture:
Protect from moisture. Protect from high humidity.

Others:
Keep in a safe place out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Uromax 5 mg tablets are green, round, film coated tablets. Each tablet is engraved with "U" on one side and a number corresponding to the mg strength on the other. They are available in opaque plastic bottles containing 100 tablets.

Uromax 10 mg tablets are yellow, round, film coated tablets. Each tablet is engraved with "U" on one side and a number corresponding to the mg strength on the other. They are available in opaque plastic bottles containing 100 tablets.

Uromax 15 mg tablets are pink, oval, film coated tablets. Each tablet is engraved with "U" on one side and a number corresponding to the mg strength on the other. They are available in opaque plastic bottles containing 100 tablets.

Composition: cetostearyl alcohol, dibasic calcium phosphate dihydrate, dye blend yellow, hydroxyethyl cellulose, magnesium stearate, methacrylic acid copolymer Type C, microcrystalline cellulose, sodium alginate, talc, triethyl citrate.

Film Coating:

5 mg: FD&C Blue No.2 Aluminum Lake, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, synthetic yellow iron oxide, titanium dioxide

10 mg: hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, synthetic yellow iron oxide, titanium dioxide

15 mg: hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, synthetic red iron oxide, titanium dioxide

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

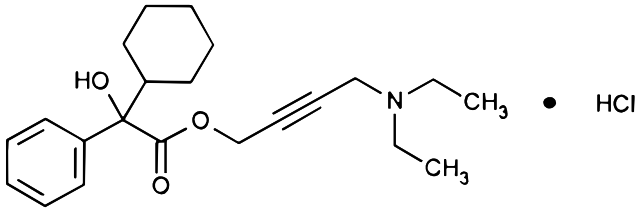
Drug Substance

Proper name: Oxybutynin Chloride

Chemical name: Benzeneacetic acid, α-cyclohexyl-α-hydroxy,-4-(diethylamino)-2-butynyl ester hydrochloride, (±)-4-(diethylamino)-2-butynyl- α-phenylcyclohexane glycolate hydrochloride

Molecular formula and molecular mass: $C_{22}H_{31}NO_3 \bullet HCl$ / 393.96

Structural formula:



Physicochemical properties: White crystalline, practically odourless powder. Freely soluble in water and in alcohol; very soluble in methanol and in chloroform; soluble in acetone; slightly soluble in ether; very slightly soluble in hexane.

Melting Point: 124 – 129˚C.

CLINICAL TRIALS

Table 4 - Summary of Patient Demographics in Clinical Trials of Patients with Urinary Incontinence

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n=number)	Mean Age (Range)	Gender
018-005	Randomized, double-blind, parallel vs. IR oxybutynin	Titration: 5, 10, 15, 20 mg/day, oral, 6 weeks	CR=53 IR=41	CR=58.0 (57.3-65.4) IR=60.6 (59.9-67.2)	CR: M=5, F=48 IR: M=4, F=37
018-009	Randomized, double-blind, parallel, dose response	Fixed dose: 5, 10 or 15 mg/day, oral, 4 weeks	5 mg=77 10 mg=77 15 mg=83	5 mg=58.1 (18.6-86.6) 10 mg=63.2 (27.8-86.5) 15 mg=61.4 (27.9-88.4)	5 mg: M=14, F=63 10 mg: M=9, F=68 15 mg: M=12, F=71

The populations enrolled in these studies are typical of the population suffering from symptoms of overactive bladder (i.e., urge incontinence, urinary frequency and urgency), in being relatively elderly (mean age in the studies ranging from 58 – 63 years) and predominantly female (87%), although a limited number (4%) of patients over the age of 80 were enrolled. The measure of drug effect was a comparison between symptoms prior to treatment and symptoms at the end of treatment. Estimates of placebo effect were not made but an efficacy comparison with a low dose reference treatment was made in the second study.

Study Results

Table 5 - Results of Study 018-005 in Patients with Urinary Incontinence

Primary Endpoints	Associated Value and Statistical Significance for Uromax vs. Baseline	Associated Value and Statistical Significance for IR Oxybutynin vs. Baseline
Urinary Incontinence *(episodes/week)*	N=51 Baseline 24.3 Uromax 10.4 57.2% reduction (p = 0.0001)	N=39 Baseline 23.0 IR oxybutynin 6.1 73.5% reduction (p = 0.0001)
	(Uromax vs. IR oxybutynin, p = 0.4036)	
Micturition Frequency *(episodes/day)*	N=51 Baseline 11.4 Uromax 9.6 15.8% reduction (p = 0.0006)	N=39 Baseline 11.0 IR oxybutynin 8.6 21.8% reduction (p = 0.0001)
	(Uromax vs. IR oxybutynin, p = 0.2852)	
Frequency of Urgency *(episodes/day)*	N=41 Baseline 3.3 Uromax 2.4 27.3% reduction (p = 0.0001)	N=29 Baseline 3.2 IR oxybutynin 1.9 40.6% reduction (p = 0.0001)
	(Uromax vs. IR oxybutynin, p = 0.1151)	

Table 5 - Results of Study 018-005 in Patients with Urinary Incontinence

Primary Endpoints	Associated Value and Statistical Significance for Uromax vs. Baseline	Associated Value and Statistical Significance for IR Oxybutynin vs. Baseline
Severity of Urgency *(1- 5 Scale)*	N=45 Baseline 3.8 Uromax 2.8 26.3% reduction (p = 0.0001)	N=32 Baseline 3.7 IR oxybutynin 2.3 37.8% reduction (p = 0.0001)
	(Uromax vs. IR oxybutynin, p = 0.2550)	
Urine Volume per Void *(mL)*	N=28 Baseline 177 Uromax 202 14.1% increase (p = 0.0631)	N=23 Baseline 221 IR oxybutynin 261 18.1% increase (p = 0.0766)
	(Uromax vs. IR oxybutynin, p = 0.5300)	

Table 6 - Results of Study 018-009 in Patients with Urinary Incontinence

	Associated Value and Statistical Significance for Uromax Dose Response*			
Primary Endpoints	**5 mg/day**	**10 mg/day**	**15 mg/day**	**p Value (dose)**
Urinary Incontinence *(episodes/day)* Baseline Uromax % reduction (p Value)	3.2 1.6 (n=74) 50% (0.0001)	2.9 1.5 (n=70) 48.3% (0.0001)	3.2 1.0 (n=74) 68.7% (0.0001)	0.0166
	p Value vs. 5 mg p Value vs. 10 mg	0.5156 -	0.0061 0.0385	
Micturition Frequency *(voids/day)* Baseline Uromax % reduction (p Value) p Value vs. 5 mg p Value vs. 10 mg	10.6 9.4 (n=74) 11.3% (0.0001)	10.2 9.1 (n=70) 10.8% (0.0001)	10.9 9.4 (n=74) 13.8% (0.0001)	0.5387
	p Value vs. 5 mg p Value vs. 10 mg	0.5815 -	0.2666 0.5831	
Overall Urinary Control *(frequency, urgency, incontinence; 0 - 4 Scale)* Uromax	1.6 (n=77)	1.9 (n=73)	2.2 (n=79)	0.0138
	p Value vs. 5 mg p Value vs. 10 mg	0.1316 -	0.0035 0.1666	
Urine Volume per Void *(mL)* Baseline Uromax % increase (p Value)	204.6 221.7 (n=65) 8.4 % (0.0097)	200.9 221.4 (n=62) 10.2% (0.0001)	214.9 259.5 (n=67) 20.8% (0.0001)	0.0423
	p Value vs. 5 mg p Value vs. 10 mg	0.5348 -	0.0163 0.0708	

* In this fixed dose randomized double-blind comparison, there was a significant difference between the low-dose reference treatment (5 mg) and Uromax 15 mg, but not 10 mg - which was also less effective than Uromax 15 mg.

Comparative Bioavailability Studies

Study 018-007 was a 4-way, analytically blinded cross-over bioavailability study of 15 mg controlled-release (single dose) and immediate release 5 mg (3 doses, q8h) oxybutynin chloride in fasting and fed volunteers. Each treatment was administered after a 10-hour fast and after a standard breakfast to 20 healthy, adult, male volunteers.

Table 7 - Single Dose Study 018-007: Mean Pharmacokinetic Parameters under Fasted Conditions

Oxybutynin 15 mg Mean (CV%) - from Measured Data				
Parameter (Arithmetic Mean)	**Uromax**	**Ditropan® (Alza, Canada)**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.hr/mL)	73.71 (54.0)	62.63 (58.0)	117.6	105.2 - 130.0
AUC_I (ng.hr/mL)	89.22 (49.3)	65.42 (58.8)	128.4	115.1 - 141.8
C_{MAX} (ng/mL)	5.22 (71.6)	8.34 (48.0)	64.5	46.9 - 82.0
T_{MAX} (hr)	11.6 (55.8)	0.84 (38.0)		
$T_{½}$ (hr)	13.2 (32.8)	5.42 (69.7)		

Table 8 – Single Dose Study 018-007: Pharmacokinetic Parameters under Fed Conditions

Oxybutynin 15 mg Mean (CV%) - from Measured Data				
Parameter (Arithmetic Mean)	**Uromax**	**Ditropan® (Alza, Canada)**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (ng.hr/mL)	64.76 (55.3)	74.40 (45.5)	87.7	77.2 – 98.2
AUC_I (ng.hr/mL)	76.54 (49.2)	81.47 (37.6)	88.5	77.8 – 99.2
C_{MAX} (ng/mL)	3.64 (52.2)	9.84 (46.2)	38.7	23.8 – 53.5
T_{MAX} (hr)	10.8 (51.8)	1.35 (43.0)		
$T_{½}$ (hr)	11.6 (46.0)	8.14 (43.4)		

Study 018-008 was a 2-way, multiple-dose cross-over bioavailability and pharmacodynamic study of 15 mg controlled release (single daily dose) and immediate release 5 mg (3 doses, q8h) oxybutynin chloride. Each treatment was administered for 5 consecutive days. All subjects were in the fasted state following a 10-hour overnight fast prior to the first dose on Days 1 and 5, and an eight hour fast on Days 2 through 4.

Table 9 - Multiple Dose Study 018-008: Pharmacokinetic Parameters at Steady State

Oxybutynin 15 mg Mean (CV%) - from Measured Data				
Parameter	**Uromax**	**Ditropan® (Alza, Canada)**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{96\text{-}120}$ (ng.hr/mL)	72.97 (52.7)	53.62 (77.8)	136.1	125.1 - 147.1
C_{MAX} (ng/mL)	5.65 (53.4)	7.53 (64.8)	75.1	61.6 - 88.5
C_{MIN} (ng/mL)	1.64 (54.2)	0.74 (98.6)	219.9	182.5 - 257.3
T_{MAX} (hr)	9.17 (44.6)	6.53 (77.9)		

DETAILED PHARMACOLOGY

The smooth muscle of the bladder (the detrusor muscle) is densely innervated by parasympathetic nerve fibres which facilitate a coordinated contraction to eliminate urine. Normal micturition is initiated by stimulation of afferent nerves which activate parasympathetic pathways innervating the bladder. The resulting release of acetylcholine activates muscarinic receptors which induces detrusor muscle contraction. At the same time, the somatic motor innervation of the external urethral sphincter is reflexly inhibited, the internal sphincter of the bladder neck also relaxes, and urine is voided.

In isolated detrusor or intact bladder preparations from several animal species, oxybutynin competitively antagonizes contractions elicited by muscarinic agents or electrical stimulation. Antagonism by oxybutynin at muscarinic receptors of the detrusor in various species has been estimated at 5 - 27 times lower than that of atropine, and 10 times lower than atropine in rat brain. Radioligand binding studies in human detrusor muscle demonstrate binding of oxybutynin to muscarinic receptors and indicate that the inhibition constant of oxybutynin is 3.3 - 25 times higher than that of atropine.

In addition to anticholinergic effects, oxybutynin has a direct relaxant effect on smooth muscle. Oxybutynin reduces both spontaneous contractions of the detrusor as well as contractions evoked by electrical stimulation, barium chloride and potassium chloride, with a potency equivalent to that of papaverine but 10 fold greater than that of atropine. This effect is not related to phosphodiesterase inhibition. It has been suggested that the direct smooth muscle relaxant effect

of oxybutynin is mediated via calcium antagonism, although this effect is less than that observed with the calcium channel blocker, verapamil.

In addition to its antispasmodic and anticholinergic effects, oxybutynin also possesses local anesthetic effects. The molecular structure of oxybutynin resembles amines with a local anesthetic effect, such as lidocaine. In vivo animal studies have suggested that oxybutynin has approximately twice the anesthetic potency of lidocaine when administered intradermally. In the rabbit cornea model, oxybutynin was approximately twice as potent as lidocaine in producing corneal anaesthesia. Smooth muscle relaxation produced by oxybutynin is thought to be related to its anesthetic activity. Many local anesthetics produce inhibition of muscle contractility as a result of their effects on cellular Ca++. Oxybutynin has been demonstrated to inhibit the inward flux of Ca++ in K+ depolarized detrusor preparations.

Studies in isolated myocytes indicate that oxybutynin has limited activity on ion channels responsible for cardiac repolarization, particularly the rapidly activating component of the delayed rectifier K+ current (I_{Kr}) that has been implicated in the mechanism of drug-induced QT interval prolongation. The IC_{50} for suppression of I_{Kr} was 11.4 µM for oxybutynin compared with 0.5 µM for terolidine and 0.05 µM for terfenadine (drugs with known potential for QT prolongation).

TOXICOLOGY

Acute toxicity studies of oxybutynin indicate that it is similar or less toxic than atropine. The LD50 for oral oxybutynin in the mouse was 725 mg/kg compared to 468 mg/kg for atropine. Sub-acute toxicity studies at 50, 100 and 150 mg/kg oxybutynin in rats have been completed for a period of 3 months. Mortality at the lower dosages did not differ significantly from that observed among controls. However, at the highest dosages there was approximately 50% mortality. There were no gross pathologic changes in tissues which could be attributed to drug administration.

In dogs, doses of 2, 4 and 8 mg/kg/day were given for 2 months. The only gross tissue changes at autopsy were inflamed areas (erythema) in the small intestine.

In 26 week studies in rats and dogs at doses 24 to 1300 times the human daily dose only minor dose-related changes were noted in the rat and none in the dog.

A 24 month study in rats at dosages up to approximately 400 times the recommended human dosage showed no evidence of carcinogenicity.

There was no increase in mutagenic activity when tested in Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae and Salmonella typhimurium test systems.

There were no abnormalities in the young born to pregnant mice that had received large doses of oxybutynin during critical days of pregnancy, and post-natal survival and development were normal. Similarly, female rats given oxybutynin prior to and during mating, gestation and lactation produced litters of normal weight, size and appearance, and growth and survival were not different from controls.

In fertility studies, female rats were dosed for 2 weeks prior to mating and thereafter up to and including day 7 of gestation at doses up to 75 mg/kg/day. There was an increased incidence of fetuses with extra thoracic ribs at the highest dose, but no effects at doses of 3 and 15 mg/kg/day.

In embryotoxicity studies in rats, dosed at 0 to100 mg/kg/day from day 7 to 17 of gestation inclusive, and in rabbits dosed at 0 to 48 mg/kg/day from day 6 to 18 of gestation, there were no adverse effects upon litter size. There was an increase in the incidence of litters with one or more pups showing extra thoracic-lumbar ribs in the rats dosed at 100 mg/kg/day.

In peri-post natal studies in the rat dosed from day 17 of gestation to day 21 post-partum, at dosages of 0 to 50 mg/kg/day there was a slight increase in pup mortality at 50 mg/kg/day. There was an absence of effects on reproductive processes at the lower doses.

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PART III: CONSUMER INFORMATION

Uromax®
Oxybutynin Chloride Controlled Release Tablets

This leaflet is part III of a three-part "Product Monograph" published when **Uromax** was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Uromax**. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Uromax is an oral tablet that slowly releases oxybutynin over a 24 hour period to control symptoms of an overactive bladder such as the frequency and urge to urinate.

What it does:
Oxybutynin relaxes the smooth muscles of the bladder to reduce the number of times you leak urine, and reduces the excessive urge and frequency to urinate which should help you live more comfortably and independently.

When it should not be used:
- If you are hypersensitive to oxybutynin or to any of the other ingredients (See "**What the important nonmedicinal ingredients are**");
- If you have any obstruction or problems with the digestive or urinary system, such as severe ulcerative colitis (chronic ulceration and inflammation of the colon);
- If you suffer from glaucoma, myasthenia gravis, megacolon;
- If your heart or circulatory status is compromised by blood loss.

What the medicinal ingredient is:
Oxybutynin Chloride

What the important nonmedicinal ingredients are:
cetostearyl alcohol, dibasic calcium phosphate dihydrate, dye blend yellow, FD&C Blue No.2 Aluminum Lake, hydroxyethyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer Type C, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium alginate, synthetic red iron oxide, synthetic yellow iron oxide, talc, titanium dioxide, triethyl citrate.

What dosage forms it comes in:
Uromax tablets are available in three strengths: 5 mg (green), 10 mg (yellow) and 15 mg (pink). It may be necessary for you to take more than one tablet at the same time, in order to receive the total daily dosage prescribed by your doctor.

WARNINGS AND PRECAUTIONS

BEFORE you use Uromax talk to your doctor or pharmacist if:
- You will be operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Driving or other tasks requiring full alertness should not be attempted until you are sure that taking **Uromax** does not make you drowsy or blur your vision.
- You expect to be exposed to a high environmental temperature or engage in hard physical work since oxybutynin may decrease sweating and cause increased body temperature and heat stroke.
- You have heart disease, thyroid disease, heartburn or esophageal reflux, diarrhea, ulcerative colitis, prostate enlargement or disease of the liver or kidneys.
- You are pregnant, trying to become pregnant, or nursing.

INTERACTIONS WITH THIS MEDICATION

Before taking **Uromax**, tell your doctor or pharmacist if you are taking or have recently taken any other medications, including those purchased without a prescription. Alcohol may increase drowsiness caused by **Uromax**.

PROPER USE OF THIS MEDICATION

You should follow the dose prescribed by your doctor.

Usual starting dose: 10 – 15 mg taken orally once a day, at about the same time each day.

Uromax may be taken with or without food.

Uromax tablets should be swallowed whole with the aid of liquids and should not be chewed, crushed or cut in half.

Overdose:
Symptoms may include restlessness, tremor, irritability, delirium, hallucinations, flushing, fever, nausea, vomiting, increased pulse, breathing difficulties, paralysis and coma.

In case of drug overdose, contact your doctor and/or your local emergency number and/or a Regional Poison Control Centre immediately, even though you may not feel sick.

Missed Dose:
If you forget to take one or more doses, take your next dose at the normal time and in the normal amount. You should not take any more than prescribed. Do not try to make up for the missed dose by taking a double dose next time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, **Uromax** may cause some side effects. The most common side effects with **Uromax** are dry mouth, sore throat or dry skin. This is to be expected so your doctor may decrease your dose while you are using **Uromax**. The intensity of your dry mouth may decrease over time while you are taking **Uromax**.

Less commonly reported side effects are listed below. Tell your doctor if you experience any of the following effects:

- Blurred vision
- Constipation
- Difficulty urinating
- Dizziness
- Drowsiness
- Headache
- Heartburn
- Nausea
- Sleeplessness
- Stomach pain
- Weakness

This is not a complete list of possible side effects. Check with your doctor or pharmacist right away if you experience any bothersome or unusual effects while taking **Uromax**.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	allergic reaction			√
	burning with urination, blood in urine, or increased urgency to void		√	√
	heart rhythm disturbance, e.g. dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat)		√	√

This is not a complete list of side effects. For any unexpected effects while taking Uromax, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15-30˚C).
Protect from exposure to light.
Protect from moisture. Protect from high humidity.
Keep in a safe place out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.purdue.ca

or by contacting the manufacturer, Purdue Pharma, at:
1-800-387-4501.

This leaflet was prepared by Purdue Pharma

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