PRODUCT MONOGRAPH

[Pr]PAT-oxybutynin chloride ER

oxybutynin chloride
Extended-release Tablets, USP
5 mg, 10 mg and 15 mg

Anticholinergic/Antispasmodic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Extended-release tablet, 5 mg, 10 mg and 15 mg	lactose *For a complete listing of nonmedicinal ingredients, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section.*

INDICATIONS AND CLINICAL USE

PAT-oxybutynin chloride Extended-release (ER) (oxybutynin chloride) is indicated for the relief of the symptoms of urge incontinence, urgency and frequency in patients with overactive bladder (U-UI).

Geriatrics (> 65 years of age):
The efficacy of PAT-oxybutynin chloride ER is similar in patients younger or older than 65 years.

Pediatrics (< 18 years of age):
The safety and efficacy of PAT-oxybutynin chloride ER in children have not been established.

CONTRAINDICATIONS

PAT-oxybutynin chloride ER is contraindicated in patients with urinary retention, gastric retention, and other severe decreased gastrointestinal motility conditions, uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

PAT-oxybutynin chloride ER is contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product. For a complete listing of the nonmedicinal ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

As with any other nondeformable material, caution should be used when administering PAT-oxybutynin chloride ER (oxybutynin chloride) to patients with pre-existing 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.

Patients should be informed that PAT-oxybutynin chloride ER should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Patients should be informed that, when administered in the presence of high environmental temperature, anticholinergics such as PAT-oxybutynin chloride ER can cause heat prostration (fever and heat stroke due to decreased sweating).

Because anticholinergic agents such as PAT-oxybutynin chloride ER may produce drowsiness (somnolence) or blurred vision, patients should be advised to exercise caution.

Alcohol or other sedative drugs may enhance the drowsiness caused by anticholinergic agents such as PAT-oxybutynin chloride ER.

Carcinogenesis and Mutagenesis

See ***Product Monograph Part II*: TOXICOLOGY, Carcinogenesis, Mutagenesis, Impairment of Fertility** for discussion on animal data.

Cardiovascular

Although there are no clinical trial or post-marketing data to confirm the potential for PAT-oxybutynin chloride ER to aggravate certain pre-existing cardiac conditions, this product is in the class of anticholinergic medications which are known to have cardiac effects. Prescribers should therefore use caution when prescribing PAT-oxybutynin chloride ER to patients with coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia or hypertension.

Although no formal QT studies have been conducted for oxybutynin formulations, there have been very rare reports of QT interval prolongation with oxybutynin use. 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.

Gastrointestinal
PAT-oxybutynin chloride ER should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Administration of PAT-oxybutynin chloride ER to patients with severe ulcerative colitis may precipitate toxic megacolon.

PAT-oxybutynin chloride ER, 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 (see **CONTRAINDICATIONS**).

PAT-oxybutynin chloride ER 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.

Genitourinary
PAT-oxybutynin chloride ER should be administered with caution to patients with clinically significant bladder obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Hepatic
PAT-oxybutynin chloride ER should be used with caution in patients with hepatic disease.

Immune
Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin chloride ER. In some cases, angioedema occurred after the first dose. Angioedema associated with upper airway swelling has the potential to become 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.

Neurologic
Oxybutynin chloride ER is associated with anticholinergic central nervous system (CNS) effects (see **ADVERSE REACTIONS – Post-Market Adverse Drug Reactions**). Patients should be monitored for signs of anticholinergic CNS effects (e.g. confusion, sedation, anxiety, nervousness, hallucinations, psychotic disorder, agitation and memory impairment), particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, drug discontinuation or dose reduction should be considered.

PAT-oxybutynin chloride ER, like other anticholinergic drugs, should be administered with caution to patients with pre-existing dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

PAT-oxybutynin chloride ER should be used with caution in patients with myasthenia gravis.

Renal
PAT-oxybutynin chloride ER should be used with caution in patients with renal disease.

Special Populations

Pregnant Women: The safety of PAT-oxybutynin chloride ER administration to women who are or who may become pregnant has not been established. Therefore, PAT-oxybutynin chloride ER should not be given to pregnant women, unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PAT-oxybutynin chloride ER is administered to a nursing woman.

Pediatrics (< 18 years of age): The safety and efficacy of PAT-oxybutynin chloride ER in children have not been established.

Geriatrics (> 65 years of age): The pharmacokinetics of PAT-oxybutynin chloride ER are similar in patients younger or older than 65 years.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse events reported were the expected side effects of anticholinergic agents which include, but are not limited to, dry mouth, constipation and blurred vision. The incidence of dry mouth was dose related.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety and efficacy of oxybutynin chloride extended-release (ER) were evaluated in a total of 580 participants who received oxybutynin chloride ER in four clinical trials (429 patients), and four pharmacokinetic studies (151 healthy volunteers). The 429 patients were treated with 5-30 mg/day for up to 4.5 months. Three of the four clinical trials allowed dose adjustments based on efficacy and adverse events and one was a fixed-dose escalation design.

Adverse events from the three controlled clinical studies and one open-label study in which 429 patients were treated with 5-30 mg/day of oxybutynin chloride ER are provided in the first column of Table 1.1. Adverse events from two additional fixed-dose, active-controlled clinical trials in which 576 patients were treated with a fixed dose of oxybutynin chloride ER 10 mg/day for a 12-week duration are provided in the second column of Table 1.1. The adverse events are reported regardless of causality.

For patients receiving 5-30 mg/day oxybutynin chloride ER, the discontinuation rate for all adverse events was 6.8%. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%). The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar.

The most common adverse events reported by the 429 patients receiving 5-30 mg/day oxybutynin chloride ER were the expected side effects of anticholinergic agents, including dry mouth, constipation, and somnolence. The incidence of all dry mouth events at doses up to 30 mg was 60.8%; 1.2% of patients treated with oxybutynin chloride ER discontinued due to dry mouth. At the fixed dose of 10 mg/day, the incidence of all dry mouth events was 29.3% of which 20.8% were mild.

Table 1.1: Incidence (%) of Adverse Events Reported by ≥ 5% of Patients Using oxybutynin chloride ER (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies

Body System	Adverse Event	Oxybutynin chloride ER 5-30 mg/day (n=429)	Oxybutynin chloride ER 10 mg/day (n=576)
General	headache	9.8	6.4
	asthenia	6.8	3.0
	pain	6.8	3.8
Digestive	dry mouth	60.8	29.3
	constipation	13.1	6.6
	diarrhea	9.1	7.8
	nausea	8.9	2.4
	dyspepsia	6.8	4.9
Nervous	somnolence	11.9	2.1
	dizziness	6.3	4.2
Respiratory	rhinitis	5.6	1.7
Special senses	blurred vision	7.7	1.6
	dry eyes	6.1	3.1
Urogenital	urinary tract infection	5.1	5.2

A complete list of pooled adverse events reported by patients participating in the 4 adjustable-dose and 2 fixed-dose studies are presented in Table 1.2. A total of 1006 subjects were treated with oxybutynin chloride ER (5-30 mg/day) from 3 to up to 23 weeks in these trials. Table 1.2 includes adverse events, regardless of investigator assessment of causality, reported by ≥1% of subjects in either treatment group. A dash represents an incidence of less than 1%. The adverse events for oxybutynin chloride immediate-release (IR) formulation, which was the comparator in three of the trials, are also presented.

Table 1.2: Adverse Events Reported by ≥ 1% of Subjects in Either Treatment Group in Clinical Trials of oxybutynin chloride ER

System/Organ Class Preferred Term	% oxybutynin chloride ER subjects reporting event (n = 1006)	% oxybutynin chloride IR subjects reporting event (n = 199)
Infections and Infestations		
Urinary tract infection	5.2	6.5
Nasopharyngitis	2.5	1.5
Upper respiratory tract infection	2.2	2.5
Sinusitis	1.7	-
Bronchitis	1.2	2.0
Cystitis	1.0	1.0
Fungal infection	--	1.0
Metabolism and Nutrition Disorders		
Fluid retention	--	1.0
Psychiatric Disorders		
Insomnia	2.8	5.5
Depression	1.7	--
Nervousness	1.5	6.5
Confusional state	1.0	2.5
Nervous System Disorders		
Headache	7.8	7.5
Somnolence	5.7	14.0
Dizziness	4.9	16.6
Dysgeusia	1.1	1.5
Sinus headache	--	2.0
Eye Disorders		
Keratoconjunctivitis sicca	4.2	2.5
Vision blurred	4.2	9.6
Eye irritation	--	1.0
Cardiac Disorders		
Palpitations	1.5	4.5
Sinus arrhythmia	--	1.0
Vascular Disorders		
Hypertension	1.3	--
Flushing	--	1.0
Respiratory, Thoracic and Mediastinal Disorders		
Nasal dryness	2.8	4.5
Cough	2.4	3.0
Pharyngolaryngeal pain	1.9	1.5
Dry throat	1.6	2.5
Sinus congestion	--	2.0
Hoarseness	--	1.0
Asthma	--	1.0
Nasal congestion	--	2.0

Table 1.2 (cont'd): Adverse Events Reported by ≥ 1% of Subjects in Either Treatment Group in Clinical Trials of oxybutynin chloride ER

System/Organ Class Preferred Term	% oxybutynin chloride ERsubjects reporting event (n = 1006)	% oxybutynin chloride IR subjects reporting event (n = 199)
Gastrointestinal Disorders		
Dry mouth	41.6	71.4
Constipation	9.1	15.1
Diarrhea	6.8	3.5
Nausea	5.2	11.6
Dyspepsia	4.7	6.0
Gastroesophageal reflux disease	1.6	--
Abdominal pain	1.5	2.5
Loose stools	1.4	3.0
Flatulence	1.2	2.5
Vomiting	1.2	1.5
Abdominal pain upper	--	3.0
Dysphagia	--	1.5
Aptyalism	--	1.0
Eructation	--	1.0
Tongue coated	--	1.0
Skin and Subcutaneous Tissue Disorders		
Dry skin	2.6	3.0
Pruritus	1.3	1.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	2.4	2.0
Arthralgia	1.5	2.0
Pain in extremity	1.3	1.0
Flank pain	--	1.0
Renal and Urinary Disorders		
Urinary retention	4.7	6.0
Urinary hesitation	2.3	8.5
Dysuria	1.7	2.5
Pollakiuria	--	1.0
General Disorders and Administration Site Conditions		
Fatigue	3.1	3.0
Edema peripheral	2.5	4.0
Asthenia	1.7	2.5
Chest pain	1.3	--
Pain	--	1.0
Thirst	--	1.0
Edema	--	1.0
Investigations		
Blood pressure increased	1.0	1.5
Blood glucose increased	--	1.5
Blood pressure decreased	--	1.0
Injury, Poisoning and Procedural Complications		
Fall	--	1.0

Note: Includes adverse events, regardless of investigator assessment of causality, reported by ≥1% of the subjects in either treatment group.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Additional adverse drug reactions reported from clinical trials with oxybutynin chloride ER with incidences < 1% and consequently not reported in Tables 1.1 or 1.2 above are listed below.

Vascular Disorders: hot flush;
Respiratory, Thoracic and Mediastinal Disorders: dysphonia, throat irritation;
Gastrointestinal Disorders: abdominal discomfort, frequent bowel movements;
Renal and Urinary Disorders: residual urine;
General Disorders and Administration Site Conditions: chest discomfort, mucosal dryness;

Post-Market Adverse Drug Reactions
Additional adverse drug reactions reported from worldwide post-marketing experience with oxybutynin chloride ER include:

Eye disorders: Glaucoma;
Immune system disorders: anaphylactic reaction, hypersensitivity;
Psychiatric Disorders: hallucinations; psychotic disorder, agitation and memory impairment;
Nervous System Disorders: convulsions;
Cardiac Disorders: arrhythmia, tachycardia;
Vascular Disorders: flushing;
Skin and Subcutaneous Tissue Disorders: rash, angioedema, urticaria;
Urogenital Disorders: impotence;
Injury, Poisoning and Procedural Complications: fall.

Other Oxybutynin Chloride Formulations
Other adverse events have been reported with other oxybutynin chloride formulations: cycloplegia, mydriasis, suppression of lactation and QT interval prolongation.

DRUG INTERACTIONS

Overview
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.

Drug-Drug Interactions
Mean oxybutynin plasma concentrations were approximately two-fold higher when oxybutynin chloride ER 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., C_{max} and AUC). The clinical

relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

Concurrent ingestion of an antacid (20 mL of an antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone) with oxybutynin chloride ER did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

Concurrent ingestion of a proton pump inhibitor (20 mg omeprazole) with oxybutynin chloride ER did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

Drug-Food Interactions
The rate and extent of absorption and metabolism of oxybutynin are similar under fed and fasted conditions.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Lifestyle Interactions
Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

DOSAGE AND ADMINISTRATION

Dosing Considerations
PAT-oxybutynin chloride ER (oxybutynin chloride) must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

PAT-oxybutynin chloride ER may be administered with or without food.

PAT-oxybutynin chloride ER should be taken at a consistent time each day.

Recommended Dose and Dosage Adjustment
Initiating Therapy
In adults, the usual starting dose of PAT-oxybutynin chloride ER is 5 or 10 mg once daily at a consistent time each day. Dosage may be adjusted in 5 mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 30 mg/day). In general, dosage adjustment may proceed at approximately weekly intervals.

Converting from Immediate-Release (IR) Formulations to PAT-oxybutynin chloride Extendend-Release (ER)
Patients already taking immediate-release oxybutynin chloride tablets may be switched to the nearest equivalent total daily dose of PAT-oxybutynin chloride ER. Patients who are not fully continent on immediate-release oxybutynin may tolerate higher doses of PAT-oxybutynin chloride ER, administered in
5 mg increments, and may achieve a greater improvement in their incontinence symptoms. Subsequent adjustment to higher or lower doses should be initiated as clinically warranted.

Missed Dose

The missed dose should be taken as soon as possible. If it is almost time for the next dose, the missed dose should not be taken. Instead, the next scheduled dose should be taken. Doses should not be doubled.

OVERDOSAGE

The continuous release of oxybutynin from PAT-oxybutynin chloride ER (oxybutynin chloride) should be considered in the treatment of overdosage. Patients should be monitored for at least 24 hours. Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PAT-oxybutynin chloride ER (oxybutynin chloride) is a tertiary amine anticholinergic agent which exerts antimuscarinic as well as direct antispasmodic action on smooth muscle. In addition to its smooth muscle relaxing effects, oxybutynin chloride exerts an analgesic and a local anesthetic effect.

Oxybutynin chloride relaxes bladder smooth muscle. In patients with uninhibited neurogenic and reflex neurogenic bladder, cystometric studies have demonstrated that oxybutynin chloride increases bladder (vesical) capacity, diminishes the frequency of uninhibited contractions of the detrusor muscle, and delays the initial desire to void. PAT-oxybutynin chloride ER thus decreases urgency and frequency of both incontinent episodes and voluntary urination.

Pharmacodynamics

Several studies have assessed oxybutynin's urodynamic effect (increase in bladder capacity) as measured by cystometry. The onset of action was rapid (within 1 h) following 5 mg oral oxybutynin chloride. The effect was seen up to 10 hours post-drug administration. Intravesical administration of oxybutynin chloride has also shown increase in bladder capacity within 1 - 1.5 h after drug instillation.

Pharmacokinetics

Absorption: Oxybutynin chloride is readily absorbed from the gastrointestinal tract. Following the first dose of oxybutynin chloride ER, oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter, steady concentrations are maintained for up to 24 hours.

The relative bioavailabilities of R- and S-oxybutynin from oxybutynin chloride ER are 156% and 187%, respectively, compared with immediate-release oxybutynin chloride tablets. The mean pharmacokinetic parameters for R- and S-oxybutynin are summarized in Table 1.3. The plasma concentration-time profiles for R- and S-oxybutynin are similar in shape; Figure 1.1 shows the profile for R-oxybutynin.

Table 1.3: Following a Single Dose of oxybutynin chloride ER 10 mg (n=43) Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters

Parameters (units)	R-Oxybutynin	S-Oxybutynin
C_{max} (ng/mL)	1.0 (0.6)	1.8 (1.0)
T_{max} (h)	12.7 (5.4)	11.8 (5.3)
$t_{1/2}$ (h)	13.2 (6.2)	12.4 (6.1)
$AUC_{(0-48)}$ (ng·h/mL)	18.4 (10.3)	34.2 (16.9)
AUC_{inf} (ng·h/mL)	21.3 (12.2)	39.5 (21.2)

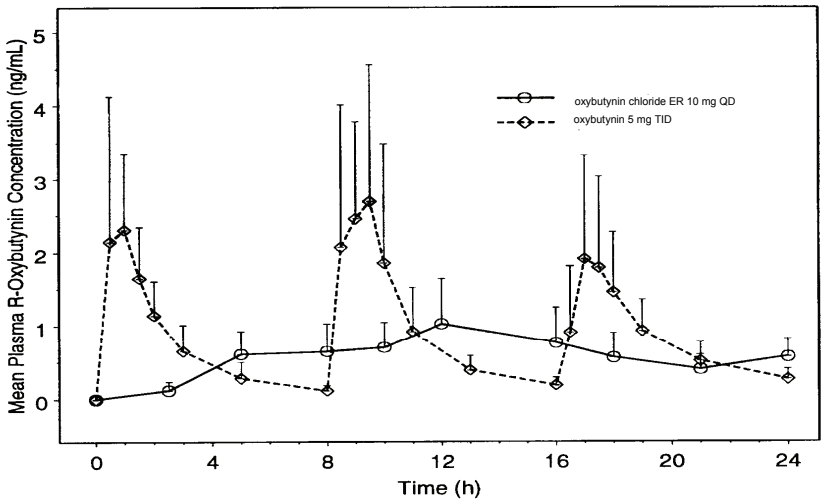


Figure 1.1. Mean R-oxybutynin plasma concentrations following a single dose of extended-release (ER) oxybutynin chloride 10 mg and immediate-release (IR) oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated oxybutynin chloride ER dosing, with no drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters. 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 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 ER administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with immediate-release oxybutynin chloride tablets.

Excretion: Oxybutynin is extensively metabolized by the liver, with less than 0.1% of the administered dose excreted unchanged in the urine.

Dose Proportionality: Pharmacokinetic parameters of oxybutynin and desethyloxybutynin (C_{max} and AUC) following administration of oxybutynin chloride ER are dose proportional.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of oxybutynin chloride ER were not evaluated in individuals younger than 18 years of age. The pharmacokinetics of immediate-release oxybutynin chloride in children (5-13 years) are similar to those in adults.

Geriatrics: The pharmacokinetics of oxybutynin chloride ER are similar in patients younger or older than 65 years. In frail elderly patients treated with immediate-release oxybutynin chloride, C_{max} and AUC values were approximately twice those in elderly patients or young adult volunteers.

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

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 ER.

Hepatic Insufficiency: There is no experience with the use of oxybutynin chloride ER in patients with hepatic insufficiency.

Renal Insufficiency: There is no experience with the use of oxybutynin chloride ER in patients with renal insufficiency.

STORAGE AND STABILITY

Store between 15 and 30°C. Protect from moisture and humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

PAT-oxybutynin chloride ER (oxybutynin chloride) round, extended-release tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink) and 15 mg (grey), imprinted with "5 XL", "10 XL" or "15 XL", respectively.

Composition

Inactive Ingredients: Each tablet contains butylated hydroxytoluene, cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene

oxide, polysorbate 80, propylene glycol, sodium chloride, synthetic iron oxides and titanium dioxide.

Packaging

Supplied in bottles of 100 tablets.

System Components and Performance

PAT-oxybutynin chloride ER uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semi-permeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice in the semi-permeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semi-permeable membrane controls the rate at which water permeates into the tablet core, which in turn controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of PAT-oxybutynin chloride ER depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Since the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

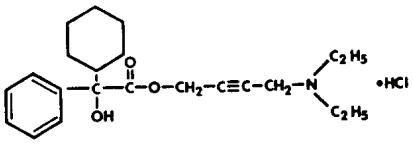
Drug Substance

Proper name: oxybutynin chloride

Chemical name: benzeneacetic acid, α-cyclohexyl-α-hydroxy-, 4-(diethylamino)-2-butynyl ester hydrochloride, (±)-. 4-(Diethylamino)-2-butynyl (±)-α-phenylcyclohexaneglycolate hydrochloride.

Molecular formula and molecular mass: $C_{22}H_{31}NO_3$ .HCl; 393.9

Structural formula:



Physicochemical properties: oxybutynin chloride is a white crystalline solid, readily soluble in water and acids, but relatively insoluble in alkalis. The melting point is 124° - 129°C.

CLINICAL TRIALS

The efficacy and safety of oxybutynin chloride ER were demonstrated in three controlled studies and one open-label study in 669 adult patients (age range 18-98 years, mean age 59 years) with urge or mixed (urge and stress) urinary incontinence. Study 1 was a forced dose-escalation design, whereas all other studies were dose-adjustment studies, in which each patient's final dose was adjusted to a balance between improvement in incontinence symptoms and tolerability (Table 2.1).

Table 2.1: Efficacy Summary of oxybutynin chloride ER Clinical Studies

Study No.	Treatment (No. of patients)	Dose mg/day	% Reduction in Urge Episodes*	% Patients Continent at Endpoint (p-value)
1	ER oxybutynin chloride (34)	5 →10 →15	90	50 (0.003 vs. placebo)
	Placebo (16)	(5 →10 →15)	49	13
	IR oxybutynin (32)	5 →10 →15	77	28 (0.06 vs. active)
2	ER oxybutynin chloride (53)	5 - 30	84	41 (0.9)
	IR oxybutynin (52)	5 - 20	88	40
3	ER oxybutynin chloride(111)	5 - 20	83	42 (0.17)
	IR oxybutynin (115)	5 - 20	76	34
4	ER oxybutynin chloride(256)	5 - 30	83	44

*All reductions are significantly different at endpoint from baseline ($p<0.01$)

Study 1
This multi-centre, randomized, double-blind, forced dose-escalation study in 82 women compared the efficacy and safety of oxybutynin chloride ER to oral placebo. Oxybutynin chloride ER was significantly more effective than placebo (p=0.001) in reducing urge incontinence episodes (from 15.9 to 1.5 episodes per week). Patients treated with oxybutynin chloride ER experienced a 90% mean decrease in weekly urge incontinence episodes (from 15.9 to 1.5 episodes per week). Significantly more patients in the oxybutynin chloride ER group than in the placebo group were completely continent (p=0.003, 50% vs. 13%, respectively). Void frequency, in terms of weekly micturitions, was reduced by a mean of 23% (from 85.2 to 65.9 micturitions per week). Mean pad usage was reduced from 12.2 per week at baseline to 2.2 at endpoint in patients treated with oxybutynin chloride ER (p<0.001 vs. placebo).

Study 2
This multi-centre, randomized, double-blind, active-control, parallel-group study in 105 men and women compared the efficacy and safety of oxybutynin chloride ER to immediate-release oxybutynin. Patients treated with oxybutynin chloride ER experienced an 84% mean decrease in weekly urge incontinence episodes. The difference in mean decrease in weekly urge incontinence episodes between oxybutynin chloride ER and oxybutynin chloride was not statistically significant (84% [from 27.3 to 4.8 per week] and 88% [from 21.3 to 3.1 per week], respectively).

The percent of patients completely continent at endpoint was comparable in the oxybutynin chloride ER group and the immediate-release oxybutynin group (41% vs. 40%, respectively). Fewer patients treated with oxybutynin chloride ER experienced moderate and severe dry mouth compared to patients treated with immediate-release oxybutynin (25% vs. 46%, respectively).

Study 3
This multi-centre, double-blind, randomized, parallel-group study in 226 men and women evaluated the safety and efficacy of oxybutynin chloride ER and immediate-release (IR) oxybutynin. Patients treated with oxybutynin chloride ER experienced an 83% mean decrease in weekly urge incontinence episodes (from 18.6 to 2.9 per week), and patients treated with immediate-release oxybutynin chloride experienced a 76% mean decrease (from 19.8 to 4.4 per week). The efficacy between the treatment groups was comparable. The percent of patients completely continent at endpoint was comparable in the oxybutynin chloride ER group and the immediate-release oxybutynin group (42% vs. 34%, respectively). Fewer patients treated with oxybutynin chloride ER experienced moderate and severe dry mouth compared to patients treated with immediate-release oxybutynin (17% vs. 26%, respectively).

Oxybutynin chloride ER demonstrated comparable efficacy to immediate-release oxybutynin chloride in all three controlled clinical trials.

A Kaplan-Meier survival analysis of two comparative trials (Studies 2, 3) demonstrated that comparable proportions of patients treated with oxybutynin chloride ER and immediate-release oxybutynin achieved complete continence at each dose level (p=0.75).

The incidences of moderate or severe dry mouth and of any severity of dry mouth in patients treated with oxybutynin chloride ER were similar to those in patients treated with 5 mg less of immediate-release oxybutynin chloride (Figure 2.1).

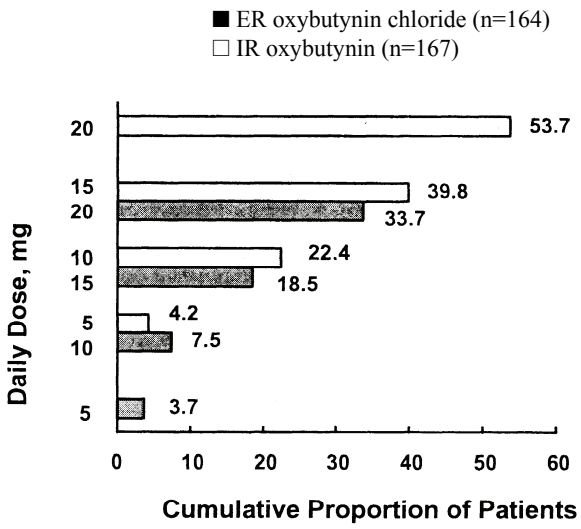


Figure 2.1. Doses at which similar proportions of patients on extended-release (ER) oxybutynin chloride and immediate-release (IR) oxybutynin report moderate or severe dry mouth.

Study 4

A noncontrolled study of 256 patients evaluated the safety and efficacy of oxybutynin chloride ER (up to 30 mg/day) for up to 23 weeks of treatment. Patients treated with oxybutynin chloride ER experienced an 83% mean decrease in weekly urge incontinence episodes. The mean number of weekly urge incontinence episodes was 18.8 at baseline, 3.9 at week 1, 2.7 at week 4, and 2.8 at end of study. At the end of the study, 44% of patients were completely continent. Void frequency was 81 micturitions per week at baseline and 67 micturitions at endpoint. Patients (n=37) being treated with immediate-release oxybutynin for urge urinary incontinence were switched to the same total dose of oxybutynin chloride ER and then dose adjusted to a balance between improvement in incontinence symptoms and tolerability.

The percent of patients achieving complete continence more than doubled, increasing from 16% at baseline on their previous medication to 46% on oxybutynin chloride ER. Patients who were treated with oxybutynin chloride ER tolerated higher doses of oxybutynin and the percentage of patients who achieved total continence increased.

DETAILED PHARMACOLOGY

Animal Pharmacology

In Vitro

In vitro studies have shown that the anticholinergic effects of oxybutynin chloride are weaker than those of atropine, but it possesses greater antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or in autonomic ganglia (no antinicotinic effects).
In a series of *in vitro* tests, oxybutynin chloride was found to be more effective than propantheline, methantheline and atropine in inhibiting barium chloride-induced contractions in rabbit bladder detrusor muscle. It was, however, less active than the other drugs in inhibiting contractions caused by histamine and carbamylcholine.

In vitro studies using preparations for rabbit vas deferens, guinea pig atria, bladder, and ileal longitudinal muscle suggest that the antimuscarinic activity resides predominantly in the R-isomer. *In vitro* studies with human detrusor preparations showed that the metabolite desethyloxybutynin has pharmacological activity similar to that of oxybutynin.

In Vivo

Oxybutynin chloride was more effective than atropine in relieving morphine-induced spasm in the anesthetized dog. Atropine had a partial effect, presumably due to the musculotropic component of its action, while methscopolamine, a neurotropic compound, was ineffective. Against neostigmine-induced spasm, oxybutynin chloride showed about 15% of the potency of atropine. These results suggest that the major antispasmodic activity of oxybutynin chloride is musculotropic rather than neurotropic.

In animal studies, the central nervous system and cardiovascular actions of oxybutynin were shown to be similar to but weaker than those of atropine.

Oxybutynin chloride was less potent than atropine in producing mydriasis in the mouse and in inhibiting the sialogogic response in dogs.

In tests for analgesic activity, oxybutynin chloride was shown to be 35% as potent as codeine in the mouse tail-clip test and approximately equal to acetylsalicylic acid in the acetic acid stretch test. It was approximately twice as potent as lidocaine in producing local anesthesia in the rabbit cornea.

Oxybutynin chloride was less potent than atropine but similar in potency to methscopolamine in producing characteristic anticholinergic CNS effects in dogs. The cardiovascular actions of oxybutynin chloride in the anesthetized dog were also relatively weak.

Using oxybutynin chloride doses at least seven times greater than the maximum recommended therapeutic dosage, the following results were obtained in various drug interaction tests: Dicumarol effects were potentiated; hexobarbital sleep time was not significantly affected; zoxazolamine paralysis time was not significantly affected; there were no effects on aniline or hexobarbital hydroxylation; O-demethylation of codeine was possibly inhibited; the nitro-reduction of codeine was possibly inhibited; the nitro-reduction of p-aminobenzoic acid was stimulated; and oxphenbutazone metabolism was not affected.

In vivo studies with volume-induced urinary bladder contractions as measured by cystometrogram in guinea pigs support *in vitro* evidence that the antimuscarinic activity resides with the R-isomer.

TOXICOLOGY

Acute Toxicity

A summary of the acute toxicity studies performed with oxybutynin chloride is presented in Table 2.2.

Table 2.2: Single-dose toxicity studies with oxybutynin chloride

Species	Route	LD_{50} (95% C.L.)*	Slope (95% C.L.)*
Mouse	P.O.	1550 mg/kg (1372-1751)	1.69 (1.48-1.93)
Mouse	I.P.	260 mg/kg (186-346)	2.2 (1.6-3.1)
Mouse	I.V.	40 mg/kg (36-45)	1.25 (1.1–1.4)
Rat	P.O.	1600 mg/kg (1176-2176)	1.94 (1.39-2.72)
Rat	I.P.	430 mg/kg (371-499)	1.32 (1.21-1.4)
Newborn Rat	P.O.	560 mg/kg (528-594)	1.07 (0.82-1.39)
Approximate Minimum Lethal Dose			
Dog	I.V.	> 25 but < 50 mg/kg	
Dog	P.O.	> 750 but < 1000 mg/kg	

* 95% confidence limits

Signs and symptoms of toxicity in mice and rats were exophthalmos, CNS stimulation, ataxia and convulsions. In rats receiving the drug orally, intraocular tension was increased in some animals at each dose level. Females were more susceptible to toxicity and mortality than males. In newborn rats, laboured respiration and decreased activity were the only toxic symptoms noted, with most deaths occurring on day 2. Mydriasis, hyperventilation, ataxia, emesis, muscular weakness of hind limbs and convulsions were commonly seen in dogs.

Subacute and Chronic Toxicity

In a three-month study, 0, 50, 100, and 150 mg/kg/day of oxybutynin chloride were administered orally to groups of 20 rats. At the highest dose, mortality was approximately 50%, while at lower doses it did not differ significantly from the control rate. Other effects observed at high dosage were ataxia, depression, hypersensitivity to stimulation and pilomotor erection.

In a six-month rat study, 20-200 mg/kg/day p.o. was administered 6 days per week. At the lowest dose no significant toxic effects were observed, while rats receiving 63-200 mg/kg/day showed signs of continuous acute pharmacologic effects, decreased food consumption with suppression of weight gain, and somewhat dose-related pathological changes consisting primarily of irregular and enlarged hepatic cells and of degenerative changes in kidney tubules.

In a two-year oral study in rats, 0, 20, 80 and 160 mg/kg/day were given to 50 animals of each sex per group. No high-dose and only a few mid-dose animals survived beyond 90 weeks.

A dose-related reduction in weight gain was observed at all dose levels. Slight mydriasis was noted in a few rats at 20 mg/kg/day and mydriasis, tenseness, hyperactivity and excessive salivation in the higher dose groups. Serum alkaline phosphatase values for most high-dose rats were slightly higher than those of controls at most intervals of analysis. Microscopic examination of the urine showed an increase in the number of red and white blood cells in mid-dose males and in the number of red cells in high-dose males at termination. No other drug-related changes were observed in hematology, ophthalmologic examinations, organ weights, gross pathology or histopathology. Tumour incidence was similar in the control and experimental groups.

A six-month study in dogs showed no toxic effects following administration of 3 and 6 mg/kg/day of oxybutynin chloride 6 days per week, while higher doses produced anorexia, tremors and nervousness during the first weeks. These signs of toxicity diminished during the remainder of the study and no other abnormalities were observed.

Groups of 4 male and 4 female beagle dogs received 0, 4, 8 and 16 mg/kg/day p.o. for one year. Dogs in the 16 mg/kg/day group were initiated at 4 mg/kg b.i.d. and the dose was gradually increased over 8 weeks to 8 mg/kg b.i.d. There were no mortalities. Dry oral mucous membranes and mydriasis were noted in all treated dogs. Some animals at 8 and 16 mg/kg/day had a dry nose, and at the highest dose level occasional increased activity, purulent ocular or nasal discharge, emaciation and/or dehydration were also observed. A dose-related decrease in body weight was seen at all dose levels, although food consumption did not differ significantly from control values.

Slightly microcytic normochromic erythrocytes were noted in a few treated dogs after one month only. Slight decreases in erythrocyte count, hemoglobin concentration and hematocrit values were noted in the 16 mg/kg/day group at all intervals of analysis. No other drug-related changes were seen in hematologic, biochemical or urinalysis values, in ophthalmoscopic examinations, or in electrocardiograms, and no gross or microscopic pathologic lesions or significant variations in organ weight were observed in any treated dogs.

A 30-day oral toxicity study examined the local gastrointestinal (GI) and systemic effects in beagle dogs that received OROS® (oxybutynin chloride) daily for 30 days. Two doses of OROS® oxybutynin were evaluated: 40 and 45 mg/d, ~3.6 or 4.1 mg/kg/d). Oxybutynin chloride ER tablets (40 mg/d, ~3.6 mg/kg/d) were used as an active comparator. There was no treatment-related GI irritation or other significant signs of systemic toxicity at doses approximately 10 times greater than the maximum proposed human dose of 30 mg/d (~0.43 mg/kg/d).

Reproductive Studies

Twenty female rats per group were administered 0, 20, and 160 mg/kg/day orally from day 6 to 16 of gestation. Dams were sacrificed on day 20 and fetuses examined. One dam in the 20 mg/kg/day group died during the gestation period. Slight mydriasis was noted at the low dose and slight to marked mydriasis and occasional tenseness at the high dose. No drug-related effects on any fetal parameters evaluated were observed at either dose level.

The teratogenic potential of oxybutynin chloride has also been studied in mice, hamsters and rabbits at doses of up to 180 mg/kg/day. No abnormalities were observed.

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

Carcinogenesis and Mutagenesis

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 surface area.

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

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PART III: CONSUMER INFORMATION

[Pr]PAT-oxybutynin chloride ER
oxybutynin chloride
Extended-release Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:
PAT-oxybutynin chloride ER is used to relieve the symptoms of overactive bladder which include the frequent and urgent need to urinate with or without urine leakage.

What it does:
PAT-oxybutynin chloride ER relaxes the smooth muscle of the bladder which results in a decreased urgency and frequency of urination and episodes of urine leakage.

When it should not be used:
You should **not** take PAT-oxybutynin chloride ER if:
- you have difficulty urinating, or stomach problems affecting passage and digestion of food;
- you have uncontrolled narrow-angle glaucoma (high pressure and pain in the eyes);
- you are allergic to oxybutynin or any of the other ingredients in PAT-oxybutynin chloride ER (see **What the nonmedicinal ingredients are**).

What the medicinal ingredient is:
oxybutynin chloride

What the nonmedicinal ingredients are:
butylated hydroxytoluene, cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, propylene glycol, sodium chloride, synthetic iron oxides and titanium dioxide

What dosage forms it comes in:
extended-release tablets: 5, 10, and 15 mg

WARNINGS AND PRECAUTIONS

BEFORE you use PAT-oxybutynin chloride ER talk to your doctor or pharmacist if you:
- have stomach problems affecting passage and digestion of food;
- have glaucoma (high pressure and pain in the eyes);
- have gastroesophageal reflux or are taking drugs (such as bisphosphonates which are used to prevent bone thinning and fractures caused by osteoporosis) that can worsen esophagitis (inflammation of the tube that connects the mouth and the stomach);
- have ulcerative colitis (inflammatory bowel disease);
- have myasthenia gravis (a muscle weakening disease);
- have heart problems;
- have kidney and liver problems;
- take certain drugs for treatment of dementia (such as Alzheimer's Disease);
- have difficulty urinating;
- are pregnant or trying to become pregnant;
- are breast-feeding.

PAT-oxybutynin chloride ER use in patients under 18 years of age has not been established.

PAT-oxybutynin chloride ER is contained within a nonabsorbable shell designed to release the drug at a controlled rate. It is normal that the shell that looks like a tablet may pass through the stomach and intestine and appears in the stool.

In hot weather, PAT-oxybutynin chloride ER can cause heat prostration (fever and heat stroke due to decreased sweating).

PAT-oxybutynin chloride ER may produce drowsiness or blurred vision. Do not drive or operate machinery until you know how the medication affects you.

Alcohol may add to the drowsiness caused by PAT-oxybutynin chloride ER.

PAT-oxybutynin chloride ER may cause central nervous system (CNS) effects (symptoms referring to changes in thinking or emotions) such as anxiety, nervousness, difficulty remembering, seeing or hearing things that are not actually there, and trouble thinking clearly or making decisions. If you experience any CNS effects, please contact your doctor immediately.

PAT-oxybutynin chloride ER may cause severe allergic reactions such as swelling of the face, lips, tongue, and upper airway that may become life-threatening.

INTERACTIONS WITH THIS MEDICATION

Always tell your doctor about all medicines you are taking. Your doctor will decide if it is safe for you to use PAT-oxybutynin chloride ER with other medicines. If you take any of the following medicines with PAT-oxybutynin chloride ER, it may affect how well they work or increase the likelihood of side effects:
- drugs that could result in serious adverse effects if small changes in dosage occur (such as digoxin for heart problems)
- other anticholinergic drugs, used to treat a number of different medical conditions (a few examples are atropine for glaucoma or hyoscine for nausea), or drugs with similar undesired effects (such as dry mouth, constipation, drowsiness, and blurred

vision)
- certain antibiotics (such as erythromycin and clarithromycin)
- certain medicines for the treatment of fungal infections (such as oral ketoconazole, itraconazole, and miconazole)

PROPER USE OF THIS MEDICATION

PAT-oxybutynin chloride ER tablets should be swallowed whole with water or liquids. **Do not chew, divide, or crush the tablets.**

PAT-oxybutynin chloride ER may be taken with or without food.

Usual dose:
The usual starting dose of PAT-oxybutynin chloride ER is 5 or
10 mg once daily at a consistent time each day. The maximum daily dose is 30 mg. Your dose may be adjusted as recommended by your doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss a dose, take it as soon as you remember. If it is almost time for the next dose, do not take the missed dose. Instead, take the next scheduled dose. 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

Like all medicines, PAT-oxybutynin chloride ER can cause side effects, although not everyone gets them. The following side effects may occur with this medicine:

Very common side effects (may affect more than 1 in 10 people):
- Dry mouth

Common side effects (affects less than 1 in 10 people):
- Pain passing urine, delay when starting to pass urine
- Urinary tract infection
- Stuffy nose (rhinitis)
- Back pain, joint pain
- Swelling feet and hands (retaining water)
- Constipation, diarrhea, indigestion, nausea, vomiting, stomach pain, flatulence, heartburn
- Problems sleeping, feeling sleepy, feeling tired
- Cough, sore or dry throat, dry nose
- Change in the way things taste
- Dry eyes, blurred eye sight
- Dry skin, itching
- Feeling dizzy
- Headache
- Chest pain
- Increased blood pressure
- Confusion, depression, nervousness

Uncommon side effects (affects less than 1 in 100 people):
- Abdominal discomfort, frequent bowel movements
- Hoarseness, throat irritation
- Flushing, hot flush
- Chest discomfort, mucosal dryness
- Bladder cannot be fully emptied (residual urine)

The following side effects have been reported with the use of PAT-oxybutynin chloride ER:
- Central nervous system (CNS) effects, their symptoms include anxiety, agitation, difficulty remembering
- Difficulty getting or keeping an erection
- Skin rash, angioedema, hives
- Falling

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	Seeing or hearing things that are not really there.			✓
	Feeling agitated, behaving irrationally and thinking abnormally.			✓
Rare	Convulsions			✓
Very Rare	Fast or uneven heartbeat.		✓	
	Allergic reaction including hives or swelling of the face, lips, tongue or throat, difficulty breathing			✓
	Glaucoma			✓

This is not a complete list of side effects. For any unexpected effects while taking PAT-oxybutynin chloride ER, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 and 30°C. Protect from moisture and humidity.

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, ON 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.patriot-canada.ca
or by contacting the sponsor, Patriot, a division of Janssen Inc., at:
1-800-567-3331 or 1-800-387-8781.

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