

OXYBUTYNYN CHLORIDE EXTENDED RELEASE TABLETS, 5 MG, 10 MG AND 15 MG

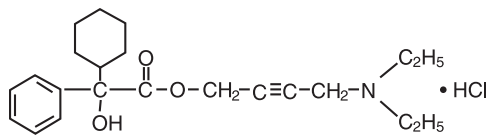
Rx only

DESCRIPTION

Oxybutynin chloride is an antispasmodic, anticholinergic agent. Each oxybutynin chloride extended release tablet contains 5 mg, 10 mg or 15 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Oxybutynin chloride is administered as a racemate of R- and S-enantiomers.

Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexyl-glycolate hydrochloride. The molecular formula of oxybutynin chloride is $C_{22}H_{33}NO_3 \cdot HCl$.

Its structural formula is:



Oxybutynin chloride is a white crystalline solid with a molecular weight of 393.9. It is readily soluble in water and acids, but relatively insoluble in alkalis.

Oxybutynin chloride extended release tablets also contain the following inactive ingredients: hydrogenated vegetable oil, hypromellose type 2208/100,000cP, isopropyl alcohol, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, talc and triethyl citrate.

System Components and Performance

Oxybutynin chloride extended release tablets employ an enteric-coated hydrophilic hydrogel matrix to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system comprises a core, which consists of the drug, rate-controlling hydrogel and other excipients. The core is surrounded by a pH-dependent membrane. In an acidic environment such as the stomach, minimal drug release will occur due to the resistance of the pH-dependent outer membrane. Upon reaching an environment of pH 5.5 and above, the outer membrane dissolves exposing the inner core tablet, which partially hydrates to form a gel layer. Drug release is via slow diffusion out of the gel layer and subsequent gel erosion.

CLINICAL PHARMACOLOGY

Oxybutynin chloride exerts a direct antispasmodic effect on smooth muscle and inhibits the muscarinic action of acetylcholine on smooth muscle. Oxybutynin chloride exhibits only one-fifth of the anticholinergic activity of atropine on the rabbit detrusor muscle, but four to ten times the antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or autonomic ganglia (antitachycardic effects).

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

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

Pharmacokinetics

Absorption

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

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

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)
$AUC_{(0-24)}$ (ng·h/mL)	18.4	(10.3)	34.2	(16.9)
AUC_{inf} (ng·h/mL)	21.3	(12.2)	39.5	(21.2)

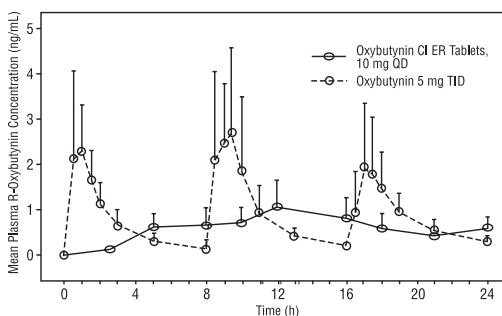


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of oxybutynin chloride extended release tablets, 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment)

Steady-state oxybutynin plasma concentrations are achieved by Day 3 of repeated oxybutynin chloride extended release tablet dosing, with no

observed drug accumulation or change in oxybutynin and desethyloxybutynin pharmacokinetic parameters.

Pharmacokinetic information for pediatric patients 5 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

Food Effects

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

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 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 extended release tablet administration, plasma concentrations of R- and S-desethyloxybutynin are 73% and 92%, respectively, of concentrations observed with oxybutynin.

Excretion

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

Dose Proportionality

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

Special Populations

Geriatric: The pharmacokinetics of oxybutynin chloride extended release tablets were similar in all patients studied (up to 78 years of age).

Pediatric: Pharmacokinetic information for pediatric patients 5 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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

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 extended release tablets.

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

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

Drug-Drug Interactions: See PRECAUTIONS: Drug Interactions.

Clinical Studies

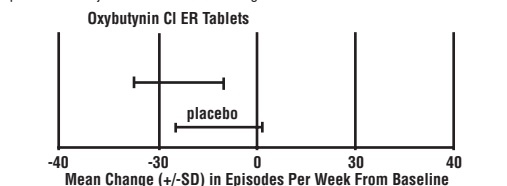
Oxybutynin chloride extended release tablets were evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 18 to 98 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge) as evidenced by ≥ 6 urge incontinence episodes per week and ≥ 10 micturitions per day. Study 1 was a forced dose escalation design, whereas the other studies used a dose adjustment design in which each patient's final dose was adjusted to a balance between improvement of incontinence symptoms and tolerability of side effects. Controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications, and these patients were maintained on a final dose for up to 2 weeks.

The efficacy results for the three controlled trials are presented in the following tables and figures.

Study 1	N	Oxybutynin CI ER Tablets	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline †	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference		(-13.6, -2.8)*		
(Oxybutynin Chloride ER Tablet- Placebo)				

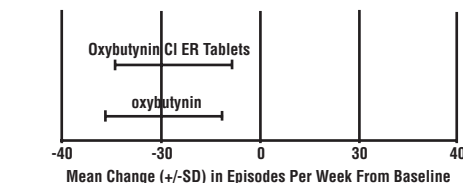
*The difference between Oxybutynin Chloride ER Tablets and placebo was statistically significant.

† Covariate adjusted mean with missing observations set to baseline values



Study 2	N	Oxybutynin CI ER Tablets	N	Oxybutynin
Mean Baseline	53	27.6	52	20.9
Mean (SD) Change from Baseline †	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference		(-2.8, 6.5)		
(Oxybutynin Chloride ER Tablet- Oxybutynin)				

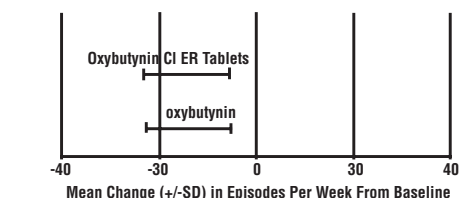
† Covariate adjusted mean with missing observations set to baseline values



Study 3	N	Oxybutynin CI ER Tablets	N	Oxybutynin
Mean Baseline	111	18.9	115	19.5
Mean (SD) Change from Baseline †	111	-14.5 (8.7)	115	-13.8 (8.6)
95% Confidence Interval for Difference		(-3.0, 1.6)**		
(Oxybutynin Chloride ER Tablet- Oxybutynin)				

** The difference between oxybutynin chloride ER tablets and oxybutynin fulfilled the criteria for comparable efficacy.

† Covariate adjusted mean with missing observations set to baseline values



INDICATIONS AND USAGE

Oxybutynin chloride extended release tablets are once-daily controlled-release tablets indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Pediatric use information for the treatment of patients aged 6 years and older with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

CONTRAINDICATIONS

Oxybutynin chloride extended release tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

Oxybutynin chloride extended release tablets are also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

Oxybutynin chloride extended release tablets should be used with caution in patients with hepatic or renal impairment and in patients with myasthenia gravis due to the risk of symptom aggravation.

Urinary Retention:

Oxybutynin chloride extended release tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see CONTRAINDICATIONS).

Gastrointestinal Disorders:

Oxybutynin chloride extended release tablets should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see CONTRAINDICATIONS).

Oxybutynin chloride extended release tablets, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony.

Oxybutynin chloride extended release tablets should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

As with any other nondeformable material, caution should be used when administering oxybutynin chloride extended release tablets to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs in nondeformable controlled-release formulations.

Information for Patients

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

Because anticholinergic agents such as oxybutynin may produce drowsiness (sommolence) or blurred vision, patients should be advised to exercise caution.

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

Patients should be informed that oxybutynin chloride extended release tablets should be swallowed whole with the aid of liquids. Patients should not chew, divide, or crush tablets.

Oxybutynin chloride extended release tablets should be taken at approximately the same time each day.

Drug Interactions

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.

Mean oxybutynin chloride plasma concentrations were approximately 2 fold higher when oxybutynin chloride extended release tablets were 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 antacid (20 mL of antacid containing aluminum hydroxide, magnesium hydroxide, and simethicone) did not significantly affect the exposure of oxybutynin or desethyloxybutynin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Oxybutynin chloride showed an increase of mutagenic activity when tested in *Schizosaccharomyces pompholiticiformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

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

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. The safety of oxybutynin chloride extended release tablet administration to women who are or who may become pregnant has not been established. Therefore, oxybutynin chloride extended release tablets should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers

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

Pediatric Use

Clinical study information for pediatric patients 6 – 15 years of age with symptoms of detrusor overactivity associated with a neurological condition (e.g., spina bifida) is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

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

Geriatric Use

The rate and severity of anticholinergic effects reported by patients less than 65 years old and those 65 years and older were similar (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations: Gender**).

ADVERSE REACTIONS

Adverse Events with Oxybutynin Chloride Extended Release Tablets

The safety and efficacy of oxybutynin chloride extended release tablets were evaluated in a total of 580 participants who received oxybutynin chloride extended release tablets in 4 clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Three of these studies allowed dose adjustments based on efficacy and adverse events and one was a fixed dose escalation design. Safety information is provided for 429 patients from three controlled clinical studies and one open label study in the first column in Table 2 below. Adverse events from two additional fixed dose,

active controlled, 12 week treatment duration, postmarketing studies, in which 576 patients were treated with oxybutynin chloride extended release tablets 10 mg/day, are also listed in Table 2 (second column). The adverse events are reported regardless of causality.

Table 2 Incidence (%) of Adverse Events Reported by $\geq 5\%$ of Patients Using Oxybutynin Chloride Extended Release Tablets (5-30 mg/day) and % of Corresponding Adverse Events in Two Fixed Dose (10 mg/day) Studies			
Body System	Adverse Event	Oxybutynin Chloride Extended-Release Tablets 5-30 mg/day (n=429)	Oxybutynin Chloride Extended-Release Tablets 10 mg/day (n=576)
General	headache	10	6
	asthenia	7	3
	pain	7	4
Digestive	dry mouth	61	29
	constipation	13	7
	diarrhea	9	7
	nausea	9	2
	dyspepsia	7	5
Nervous	somnolence	12	2
	dizziness	6	4
Respiratory	rhinitis	6	2
Special senses	blurred vision	8	1
	dry eyes	6	3
Urogenital	urinary tract infection	5	5

The most common adverse events reported by patients receiving 5-30 mg/day of oxybutynin chloride extended release tablets were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

The discontinuation rate for all adverse events was 6.8% in the 429 patients from the 4 studies of efficacy and safety who received 5-30 mg/day. The most frequent adverse event causing early discontinuation of study medication was nausea (1.9%), while discontinuation due to dry mouth was 1.2%.

In addition, the following adverse events were reported by 2 to <5% of the 429 patients who received 5-30 mg/day of oxybutynin chloride extended release tablets in the 4 efficacy and safety studies. *General*: abdominal pain, dry nasal and sinus mucous membranes, accidental injury, back pain, flu syndrome; *Cardiovascular*: hypertension, palpitation, vasodilatation; *Digestive*: flatulence, gastroesophageal reflux; *Musculoskeletal*: arthritis; *Nervous*: insomnia, nervousness, confusion; *Respiratory*: upper respiratory tract infection, cough, sinusitis, bronchitis, pharyngitis; *Skin*: dry skin, rash; *Urogenital*: impaired urination (hesitancy), increased post void residual volume, urinary retention, cystitis.

Additional rare adverse events reported from worldwide post-marketing experience with oxybutynin chloride extended release tablets include: peripheral edema, cardiac arrhythmia, tachycardia, hallucinations, convulsions, and impotence.

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

OVERDOSAGE

The continuous release of oxybutynin from oxybutynin chloride extended

release tablets 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 central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

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

DOSE AND ADMINISTRATION

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

Oxybutynin chloride extended release tablets may be administered with or without food.

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

Pediatric patients: Dosing information for pediatric patients aged 6 years and older is approved for Alza Corporation's oxybutynin chloride extended release tablets. However, due to Alza Corporation's marketing exclusivity rights, this drug product is not labeled for pediatric use.

HOW SUPPLIED

Oxybutynin chloride extended-release tablets, 5 mg—Each purple, film-coated, round convex tablets, debossed with "G 341" on one side and plain on the other side

Bottles of 100 NDC 0093-5206-01

Oxybutynin chloride extended-release tablets, 10 mg—Each pink, film-coated, round convex tablets, debossed with "G 342" on one side and plain on the other side

Bottles of 100 NDC 0093-5207-01

Oxybutynin chloride extended-release tablets, 15 mg—Each off-white, film-coated, round convex tablets, debossed with "G 343" on one side and plain on the other side

Bottles of 100 NDC 0093-5208-01

Store at 20°-25°C (68°-77°F)[see USP Controlled Room Temperature]. Protect from moisture and humidity.

Dispense in a tightly-closed, light-resistant container (USP).

Manufactured By:
IMPAX Laboratories, Inc.
Hayward, CA 94544 USA

Manufactured For:

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960



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