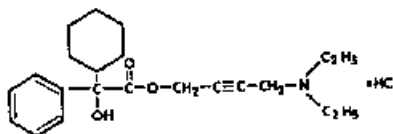


NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

DITROPAN[®]
(oxybutynin chloride)
Tablets and Syrup

DESCRIPTION

Each scored biconvex, engraved blue DITROPAN[®] (oxybutynin chloride) Tablet contains 5 mg of oxybutynin chloride. Each 5 mL of DITROPAN Syrup contains 5 mg of oxybutynin chloride. Chemically, oxybutynin chloride is d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is C₂₂H₃₁NO₃•HCl. The structural formula appears below:



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.

DITROPAN Tablets

Also contains: calcium stearate, FD&C Blue #1 Lake, lactose, and microcrystalline cellulose.

DITROPAN Syrup

Also contains: citric acid, FD&C Green #3, glycerin, methylparaben, flavor, sodium citrate, sorbitol, sucrose, and water.

DITROPAN Tablets and Syrup are for oral administration.

Therapeutic Category: Antispasmodic, anticholinergic.

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 (antinicotinic effects).

Oxybutynin chloride relaxes bladder smooth muscle. In patients with conditions characterized by involuntary bladder contractions, 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. Oxybutynin chloride thus decreases urgency and the frequency of both incontinent episodes and voluntary urination.

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

Pharmacokinetics

Absorption

Following oral administration of DITROPAN, oxybutynin is rapidly absorbed achieving C_{max} within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
 NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

reported to be about 6% (range 1.6 to 10.9%) for both the tablet and syrup. Wide interindividual variation in pharmacokinetic parameters is evident following oral administration of 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.

Table 1
 Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters
 Following Three doses of Ditropan 5 mg administered every 8 hours (n=23)

	R-oxybutynin	S-oxybutynin
Parameters (units)		
C _{max} (ng/mL)	3.6 (2.2)	7.8 (4.1)
T _{max} (h)	0.89 (0.34)	0.65 (0.32)
AUC _t (ng·h/mL)	22.6 (11.3)	35.0 (17.3)
AUC _{inf} (ng·h/mL)	24.3 (12.3)	37.3 (18.7)

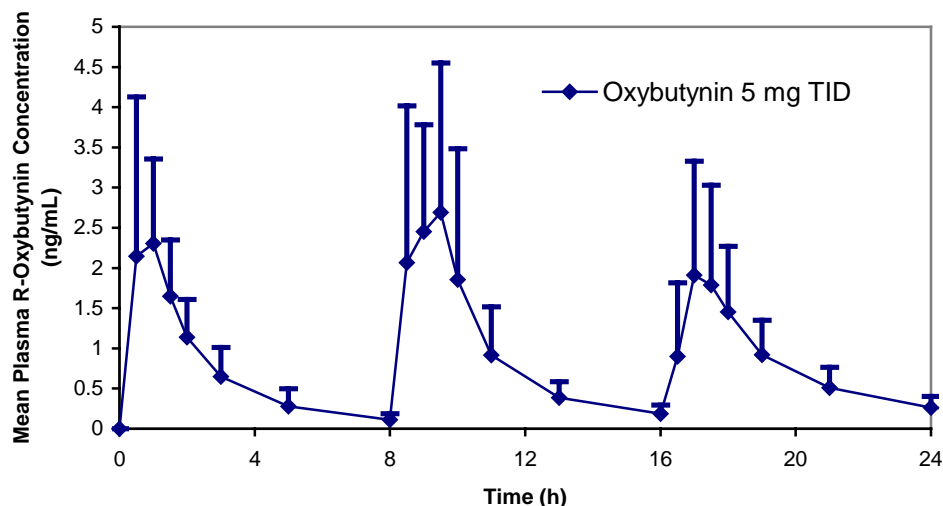


Figure 1. Mean R-oxybutynin plasma concentrations following three doses of DITROPAN[®] 5 mg administered every 8 hours for 1 day in 23 healthy adult volunteers

DITROPAN[®] steady-state pharmacokinetics was also studied in 23 pediatric patients with detrusor overactivity associated with a neurological condition (e.g., spina bifida). These pediatric patients were on Ditropan tablets (n=11) with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 mg/kg) or Ditropan syrup (n=12) with total daily dose ranging from 5 mg to 22.5 mg (0.26 to 0.75 mg/kg). Overall, most patients (86.9%) were taking a total daily Ditropan dose between 10 mg and 15 mg. Sparse sampling technique was used to obtain serum samples. When all available data are normalized to

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
 NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

an equivalent of 5 mg twice daily Ditropan, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2a (for tablet) and Table 2b (for syrup). The plasma-time concentration profile for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg twice daily.

Table 2a
Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters
In Children Aged 5-15
Following Administration of 7.5 mg to 15 mg Total Daily Dose of Ditropan Tablets (N=11)

All Available Data Normalized to An Equivalent of Ditropan Tablets 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C _{max} * (ng/mL)	6.1 ± 3.2	10.1 ± 7.5	55.4 ± 17.9	28.2 ± 10.0
T _{max} (hr)	1.0	1.0	2.0	2.0
AUC** (ng.hr/mL)	19.8 ± 7.4	28.4 ± 12.7	238.8 ± 77.6	119.5 ± 50.7

*Reflects C_{max} for pooled data

**AUC_{0-end of dosing interval}

Table 2b
Mean ± SD R- and S-oxybutynin and R- and S-desethyloxybutynin Pharmacokinetic Parameters
In Children Aged 5-15
Following Administration of 5 mg to 22.5 mg Total Daily Dose of Ditropan Syrup (N=12)

All Available Data Normalized to An Equivalent of Ditropan Syrup 5 mg BID or TID at Steady State

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C _{max} * (ng/mL)	5.7 ± 6.2	7.3 ± 7.3	54.2 ± 34.0	27.8 ± 20.7
T _{max} (hr)	1.0	1.0	1.0	1.0
AUC** (ng.hr/mL)	16.3 ± 17.1	20.2 ± 20.8	209.1 ± 174.2	99.1 ± 87.5

*Reflects C_{max} for pooled data

**AUC_{0-end of dosing interval}

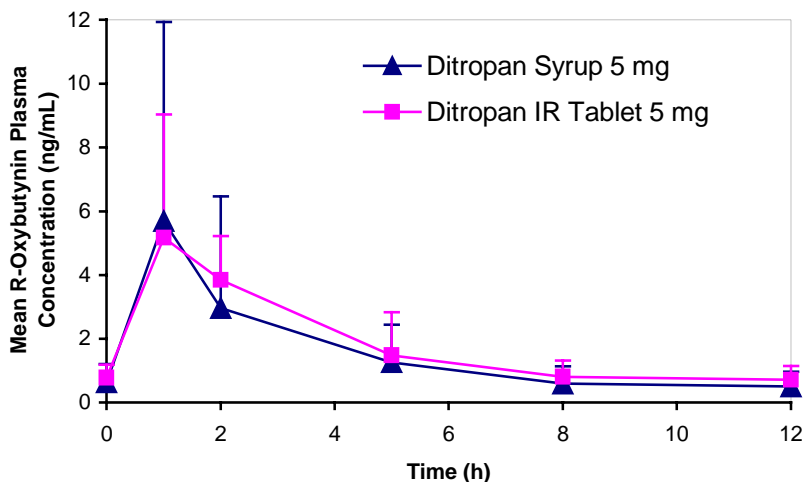


Figure 2. Mean steady-state (\pm SD) R-oxybutynin plasma concentrations following administration of total daily Ditropan dose of 5 mg to 30 mg (0.21 mg/kg to 0.77 mg/kg) in children 5-15 years of age. – Plot represents all available data normalized to the equivalent of Ditropan 5 mg BID or TID at steady state

Food effects

Data in the literature suggests that oxybutynin solution co-administered with food resulted in a slight delay in absorption and an increase in its bioavailability by 25% (n=18).¹

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.

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.

Clinical Studies

DITROPAN[®] was well tolerated in patients administered the drug in controlled studies of 30 days' duration and in uncontrolled studies in which some of the patients received the drug for 2 years.

¹ Yong C et al. Effect of Food on the Pharmacokinetics of Oxybutynin in normal subjects. *Pharm Res.* 1991; 8 (Suppl.): S-320

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

INDICATIONS AND USAGE

DITROPAN[®] (oxybutynin chloride) is indicated for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

DITROPAN 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.

DITROPAN is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN should be used with caution in the frail elderly, in patients with hepatic or renal impairment, and in patients with myasthenia gravis.

DITROPAN may aggravate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, myasthenia gravis, and prostatic hypertrophy.

Urinary Retention

DITROPAN should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (See **CONTRAINDICATIONS**).

Gastrointestinal Disorders

DITROPAN should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Administration of DITROPAN 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.

DITROPAN, 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.

DITROPAN 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.

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.

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence) 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.

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 3-4 fold higher when DITROPAN[®] (oxybutynin chloride) was administered with ketoconazole, a potent CYP3A4 inhibitor.

Other inhibitors of the cytochrome P450 3A4 enzyme system, such as antimycotic agents (e.g., itraconazole and miconazole) or macrolide antibiotics (e.g., erythromycin and clarithromycin), may alter oxybutynin mean pharmacokinetic parameters (i.e., C_{max} and AUC). The clinical relevance of such potential interactions is not known. Caution should be used when such drugs are co-administered.

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

Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility.

Pregnancy

Category B. Reproduction studies using oxybutynin chloride in the hamster, rabbit, rat, and mouse have shown no definite evidence of impaired fertility or harm to the animal fetus. The safety of DITROPAN administered to women who are or who may become pregnant has not been established. Therefore, DITROPAN 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 this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DITROPAN is administered to a nursing woman.

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

Pediatric Use

The safety and efficacy of DITROPAN[®] (oxybutynin chloride) administration have been demonstrated for pediatric patients 5 years of age and older (see DOSAGE AND ADMINISTRATION).

The safety and efficacy of Ditropan Tablets and Ditropan Syrup were studied in 30 and in 26 children, respectively, in a 24-week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that the administration of DITROPAN was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5 mg to 15 mg, treatment with Ditropan Tablets was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with Ditropan[®] Tablets was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H₂O to 33 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 39% to 20%.

At total daily doses ranging from 5 mg to 30 mg, treatment with Ditropan Syrup was associated with an increase from baseline in mean urine volume per catheterization from 113 mL to 133 mL, an increase from baseline in mean urine volume after morning awakening from 143 mL to 165 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 34% to 63%. Urodynamic results were consistent with these clinical results. Treatment with Ditropan Syrup was associated with an increase from baseline in maximum cystometric capacity from 192 mL to 294 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 46 cm H₂O to 37 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 67% to 28%.

As there is insufficient clinical data for pediatric populations under age 5, DITROPAN is not recommended for this age group.

Geriatric Use

Clinical studies of DITROPAN did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between healthy elderly and younger patients; however, a lower initial starting dose of 2.5 mg given 2 or 3 times a day has been recommended for the frail elderly due to a prolongation of the

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
 NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

elimination half-life from 2-3 hours to 5 hours.^{2,3,4} In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The safety and efficacy of DITROPAN[®] (oxybutynin chloride) was evaluated in a total of 199 patients in three clinical trials comparing DITROPAN with DITROPAN XL (see Table 3). These participants were treated with DITROPAN 5-20 mg/day for up to 6 weeks. Table 3 shows the incidence of adverse events judged by investigator to be at least possibly related to treatment and reported by at least 5% of patients.

Table 3
Incidence (%) of Adverse Events Reported by > 5% of Patients
Using DITROPAN (5-20 mg/day)

Body System	Adverse Event	DITROPAN (5-20 mg/day) (n=199)
General	Abdominal pain	6.5%
	Headache	6.0%
Digestive	Dry mouth	71.4%
	Constipation	12.6%
	Nausea	10.1%
	Dyspepsia	7.0%
	Diarrhea	5.0%
Nervous	Dizziness	15.6%
	Somnolence	12.6%
Special senses	Blurred vision	9.0%
Urogenital	Urination impaired	10.6%
	Post void residuals increase	5.0%
	Urinary tract infection	5.0%

The most common adverse events reported by patients receiving DITROPAN[®] 5-20 mg/day were the expected side effects of anticholinergic agents. The incidence of dry mouth was dose-related.

In addition, the following adverse events were reported by 2 to <5% of patients using DITROPAN (5-20 mg/day) in all studies. *General:* asthenia, dry nasal and sinus mucous

² Hughes KM et al. Measurement of oxybutynin and its *N*-desethyl metabolite in plasma, and its application to pharmacokinetic studies in young, elderly and frail elderly volunteers. *Xenobiotica*. 1992; 22 (7): 859-869.

³ Ouslander J et al. Pharmacokinetics and Clinical Effects of Oxybutynin in Geriatric Patients. *J. Urol*. 1988; 140: 47-50

⁴ Yarker Y et al. Oxybutynin: A review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapeutic Use in Detrusor Instability. *Drugs & Aging*. 1995; 6 (3): 243-262.

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

membranes; *Cardiovascular*: palpitation; *Metabolic and Nutritional System*: peripheral edema; *Nervous System*: insomnia, nervousness, confusion; *Skin*: dry skin; *Special Senses*: dry eyes, taste perversion.

Other adverse events that have been reported include: tachycardia, hallucinations, cycloplegia, mydriasis, impotence, suppression of lactation, vasodilatation, rash, decreased gastrointestinal motility, flatulence, urinary retention, convulsions and decreased sweating.

OVERDOSAGE

Treatment should be symptomatic and supportive. Activated charcoal as well as a cathartic may be administered.

Overdosage with oxybutynin chloride has been associated with anticholinergic effects including central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium, hallucinations), flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Other symptoms may include hypotension or hypertension, respiratory failure, paralysis, and coma.

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.

DOSAGE AND ADMINISTRATION

Tablets

Adults: The usual dose is one 5-mg tablet two to three times a day. The maximum recommended dose is one 5-mg tablet four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one 5-mg tablet two times a day. The maximum recommended dose is one 5-mg tablet three times a day.

Syrup

Adults: The usual dose is one teaspoon (5 mg/5 mL) syrup two to three times a day. The maximum recommended dose is one teaspoon (5 mg/5 mL) syrup four times a day. A lower starting dose of 2.5 mg two or three times a day is recommended for the frail elderly.

Pediatric patients over 5 years of age: The usual dose is one teaspoon (5 mg/5 mL) syrup two times a day. The maximum recommended dose is one teaspoon (5 mg/5mL) syrup three times a day.

HOW SUPPLIED

DITROPAN[®] (oxybutynin chloride) Tablets are supplied in bottles of 100 tablets (NDC 17314-9200-1). Blue scored tablets (5 mg) are engraved with DITROPAN on one side with 92 and 00, separated by a horizontal score, on the other side.

NDA 17-577 DITROPAN[®] (oxybutynin chloride) Tablets (Final Draft submitted 4/9/2003)
NDA 18-211 DITROPAN[®] (oxybutynin chloride) Syrup (Final Draft submitted 4/9/2003)

DITROPAN[®] Syrup (5 mg/5 mL) is supplied in bottles of 16 fluid ounces (473 mL) (NDC 17314-9201-4).

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.
Store at controlled room temperature (59-86°F).

Rx ONLY

Manufactured by Aventis Pharmaceuticals, Inc., Kansas City, MO 64137

Distributed and Marketed by Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ 08869.

Placeholder for Ortho-
McNeil Pharmaceutical,
Inc. Logo

Edition: 03/03

50017115

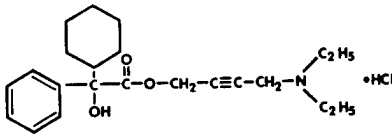
DITROPAN XL[®] (oxybutynin chloride) Extended Release Tablets

DESCRIPTION

DITROPAN XL[®] (oxybutynin chloride) is an antispasmodic, anticholinergic agent. Each DITROPAN XL 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 phenylcyclohexylglycolate hydrochloride. The empirical formula of oxybutynin chloride is $C_{22}H_{31}NO_3 \cdot HCl$.

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.

DITROPAN XL also contains the following inert ingredients: cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

System Components and Performance

DITROPAN XL 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 semipermeable 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 semipermeable 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 semipermeable 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 DITROPAN XL 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.

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 (antinicotinic 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 DITROPAN XL[®] (oxybutynin chloride), oxybutynin plasma concentrations rise for 4 to 6 hours; thereafter steady concentrations are maintained for up to 24 hours, minimizing fluctuations between peak and trough concentrations associated with oxybutynin.

The relative bioavailabilities of R- and S-oxybutynin from DITROPAN XL 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.

Table 1
Mean (SD) R- and S-Oxybutynin Pharmacokinetic Parameters
Following a Single Dose of DITROPAN XL 10 mg (n=43)

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)

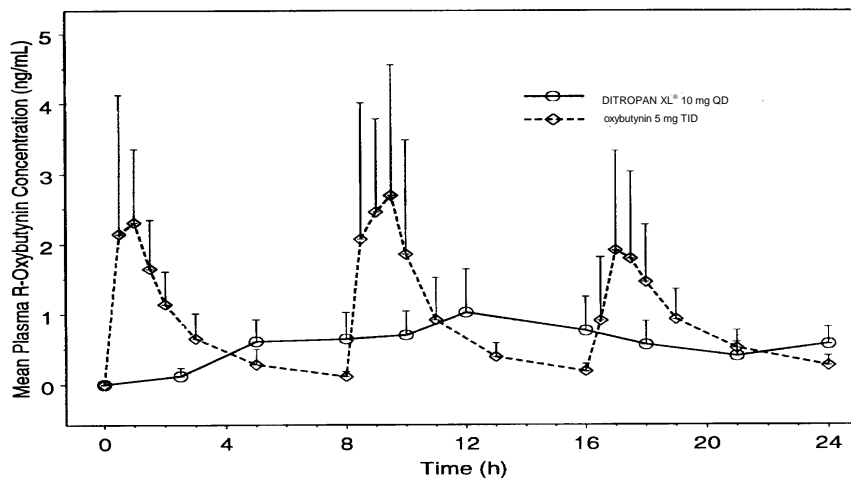


Figure 1. Mean R-oxybutynin plasma concentrations following a single dose of DITROPAN XL 10 mg and oxybutynin 5 mg administered every 8 hours (n=23 for each treatment).

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

DITROPAN XL steady-state pharmacokinetics was studied in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g. spina bifida). The children were on DITROPAN XL total daily dose ranging from 5 to 20 mg (0.10 to 0.77 mg/kg). Sparse sampling technique was used to obtain serum samples. When all available data are normalized to an equivalent of 5mg per day Ditropan XL, the mean pharmacokinetic parameters derived for R- and S-oxybutynin and R- and S-desethyloxybutynin are summarized in Table 2. The plasma-time concentration profiles for R- and S-oxybutynin are similar in shape; Figure 2 shows the profile for R-oxybutynin when all available data are normalized to an equivalent of 5 mg per day.

Table 2
Mean ± SD R- and S-Oxybutynin and R- and S-Desethyloxybutynin Pharmacokinetic Parameters in Children Aged 5-15 Following Administration of 5 to 20mg Ditropan XL Once Daily (N=19)

All Available Data Normalized To An Equivalent of Ditropan XL 5 mg Once Daily

	R-Oxybutynin	S-Oxybutynin	R- Desethyloxybutynin	S- Desethyloxybutynin
C _{max} (ng/mL)	0.7 ± 0.4	1.3 ± 0.8	7.8 ± 3.7	4.2 ± 2.3
T _{max} (hr)	5.0	5.0	5.0	5.0
AUC (ng.hr/mL)	12.8 ± 7.0	23.7 ± 14.4	125.1 ± 66.7	73.6 ± 47.7

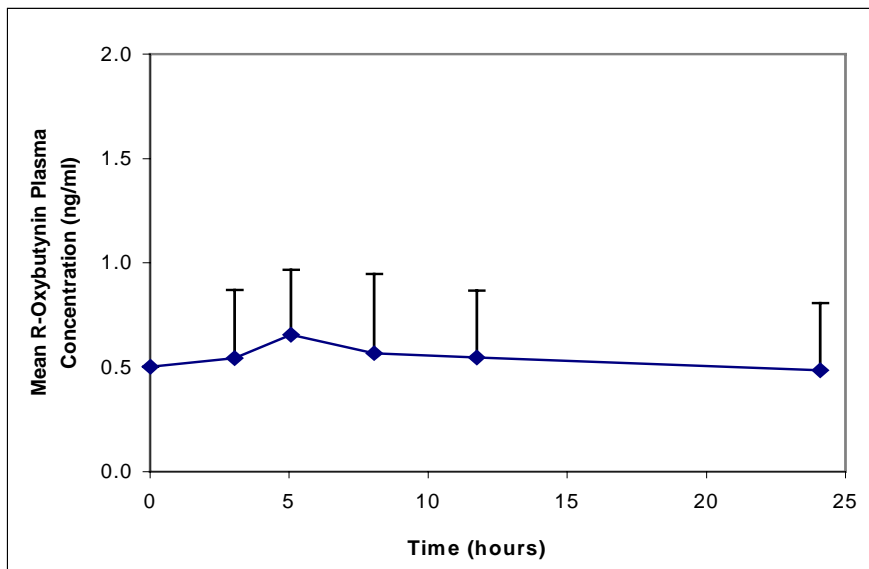


Figure 2. Mean steady state (\pm SD) R-oxybutynin plasma concentrations following administration of 5 to 20 mg Ditropan XL once daily in children aged 5-15. - Plot represents all available data normalized to an equivalent of Ditropan XL 5 mg once daily

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 DITROPAN XL 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 DITROPAN XL are dose proportional.

Special Populations

Geriatric: The pharmacokinetics of DITROPAN XL® were similar in all patients studied (up to 78 years of age).

Pediatric: The pharmacokinetics of DITROPAN XL (oxybutynin chloride) were evaluated in 19 children aged 5-15 years with detrusor overactivity associated with a neurological condition (e.g., spina bifida). The pharmacokinetics of DITROPAN XL in these pediatric patients were consistent with those reported for adults (see Tables 1 and 2, and Figures 1 and 2 above).

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

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of DITROPAN XL.

Renal Insufficiency: There is no experience with the use of DITROPAN XL in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of DITROPAN XL in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS:** Drug Interactions.

Clinical Studies

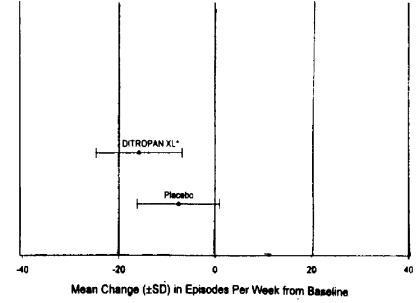
DITROPAN XL was evaluated for the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in three controlled studies and one open label study. The majority of patients were Caucasian (89.0%) and female (91.9%) with a mean age of 59 years (range, 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.

Number of Urge Urinary Incontinence Episodes Per Week

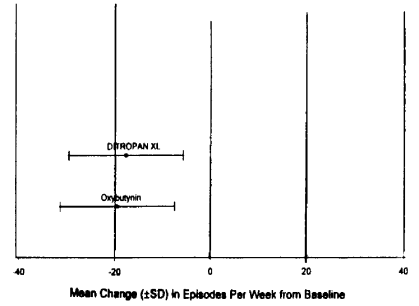
Study 1	N	DITROPAN® XL	N	Placebo
Mean Baseline	34	15.9	16	20.9
Mean (SD) Change from Baseline†	34	-15.8 (8.9)	16	-7.6 (8.6)
95% Confidence Interval for Difference (DITROPAN® XL – Placebo)				(-13.6, -2.8)*

* The difference between DITROPAN® XL and placebo was statistically significant.
 † Covariate adjusted mean with missing observations set to baseline values



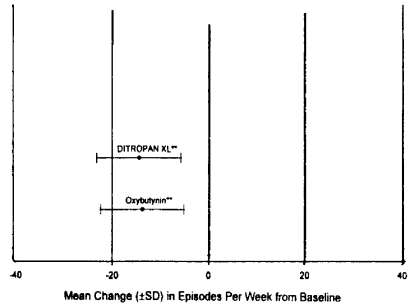
Study 2	N	DITROPAN® XL	N	oxybutynin
Mean Baseline	53	27.6	52	23.0
Mean (SD) Change from Baseline†	53	-17.6 (11.9)	52	-19.4 (11.9)
95% Confidence Interval for Difference (DITROPAN® XL – oxybutynin)				(-2.8, 6.5)

† Covariate adjusted mean with missing observations set to baseline values



Study 3	N	DITROPAN® XL	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 (DITROPAN® XL – oxybutynin)				(-3.0, 1.6)**

** The difference between DITROPAN® XL and oxybutynin fulfilled the criteria for comparable efficacy.
 † Covariate adjusted mean with missing observations set to baseline values



INDICATIONS AND USAGE

DITROPAN XL® (oxybutynin chloride) is a once-daily controlled-release tablet indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

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

CONTRAINDICATIONS

DITROPAN XL 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.

DITROPAN XL is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

PRECAUTIONS

General

DITROPAN XL 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:

DITROPAN XL should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention (see **CONTRAINDICATIONS**).

Gastrointestinal Disorders:

DITROPAN XL should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

DITROPAN XL, 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.

DITROPAN XL 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 DITROPAN XL 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 (somnolence) 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 DITROPAN XL® (oxybutynin chloride) 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.

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 DITROPAN XL 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.

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

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no 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 DITROPAN XL administration to women who are or who may become pregnant has not been established. Therefore, DITROPAN XL 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 DITROPAN XL[®] (oxybutynin chloride) is administered to a nursing woman.

Pediatric Use

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

Urodynamic results were consistent with clinical results. Administration of DITROPAN XL resulted in an increase from baseline in mean maximum cystometric capacity from 185 mL to 254 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 44 cm H₂O to 33 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 60% to 28%.

DITROPAN XL is not recommended in pediatric patients who can not swallow the tablet whole without chewing, dividing, or crushing, or in children under the age of 6 (**see DOSAGE AND ADMINISTRATION**).

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 DITROPAN XL[®]

The safety and efficacy of DITROPAN XL was evaluated in a total of 580 participants who received DITROPAN XL in clinical trials (429 patients, 151 healthy volunteers). These participants were treated with 5-30 mg/day for up to 4.5 months. Safety information is provided for 429 patients from three controlled clinical studies and one open label study (Table 3). The adverse events are reported regardless of causality.

Table 3
Incidence (%) of Adverse Events Reported by \geq 5% of Patients
Using DITROPAN XL (5-30 mg/day)

Body System	Adverse Event	DITROPAN XL 5-30 mg/day (n=429)
General	headache	9.8
	asthenia	6.8
	pain	6.8
Digestive	dry mouth	60.8
	constipation	13.1
	diarrhea	9.1
	nausea	8.9
	dyspepsia	6.8
Nervous	somnolence	11.9
	dizziness	6.3
Respiratory	rhinitis	5.6
Special senses	blurred vision	7.7
	dry eyes	6.1
Urogenital	urinary tract infection	5.1

The most common adverse events reported by patients receiving 5-30 mg/day DITROPAN XL[®] 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%. 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 patients using DITROPAN XL (oxybutynin chloride) (5-30 mg/day) in all 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 DITROPAN XL 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 DITROPAN XL (oxybutynin chloride) should be considered in the treatment of overdose. 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 chloride has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention.

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

DOSAGE AND ADMINISTRATION

DITROPAN XL[®] must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.

DITROPAN XL[®] may be administered with or without food.

Adults: The recommended starting dose of DITROPAN XL[®] is 5 mg once daily. 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 aged 6 years of age and older: The recommended starting dose of DITROPAN XL is 5 mg once daily. Dosage may be adjusted in 5-mg increments to achieve a balance of efficacy and tolerability (up to a maximum of 20 mg/day).

HOW SUPPLIED

DITROPAN XL[®] (oxybutynin chloride) Extended Release Tablets are available in three dosage strengths, 5 mg (pale yellow), 10 mg (pink) and 15 mg (gray) and are imprinted with “5 XL”, “10 XL” or “15 XL”. DITROPAN XL[®] (oxybutynin chloride) Extended Release Tablets are supplied in bottles of 100 tablets.

5 mg	100 count bottle	NDC 17314-8500-1
10 mg	100 count bottle	NDC 17314-8501-1
15 mg	100 count bottle	NDC 17314-8502-1

Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and humidity.

Rx only

For more information call 1-888-395-1232 or visit www.DitropanXL.com

Manufactured by
ALZA Corporation, Mountain View, CA 94043.



An ALZA OROS[®]
Technology Product

DITROPAN XL[®] and OROS[®] are registered trademarks of ALZA Corporation.

Distributed and Marketed by
Ortho-McNeil Pharmaceuticals, Inc., Raritan, NJ 08869.

[Placeholder for Ortho-McNeil
Pharmaceuticals, Inc. Logo](#)

00096532

Edition: 3/03

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
4/15/03 03:42:56 PM