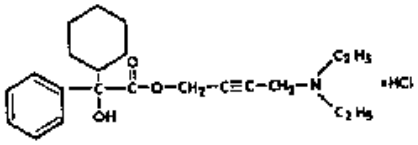
DITROPAN®
(oxybutynin chloride)
Tablets

DESCRIPTION

Each scored biconvex, engraved blue DITROPAN® (oxybutynin chloride) Tablet 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 $C_{22}H_{31}NO_3 \bullet HCl$. 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 contain calcium stearate, FD&C Blue #1 Lake, lactose, and microcrystalline cellulose.

DITROPAN Tablets 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

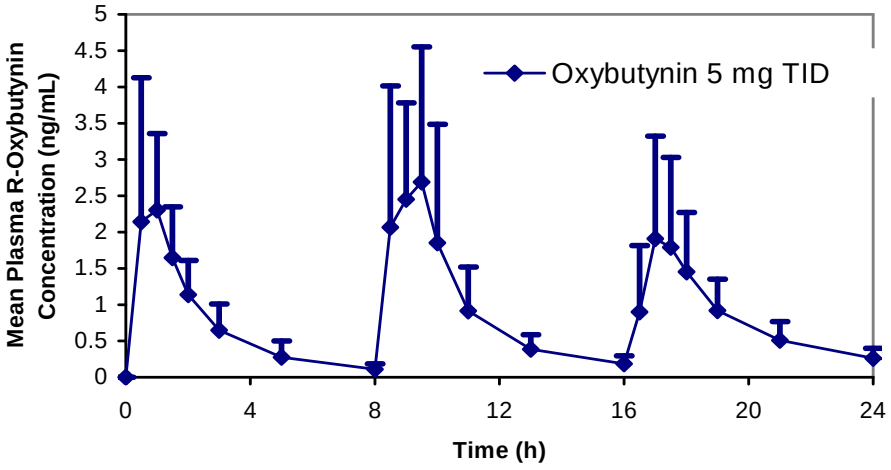
Following oral administration of DITROPAN, oxybutynin is rapidly absorbed achieving C_{max} within an hour, following which plasma concentration decreases with an effective half-life of approximately 2 to 3 hours. The absolute bioavailability of oxybutynin is reported to be about 6% (range 1.6 to 10.9%) for the tablets. 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)

Parameters (units)	R-Oxybutynin	S-Oxybutynin
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 were also studied in 11 pediatric patients with detrusor overactivity associated with a neurological condition (e.g., spina bifida). These pediatric patients were on DITROPAN tablets with total daily dose ranging from 7.5 mg to 15 mg (0.22 to 0.53 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 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 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 twice daily.

Table 2 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)

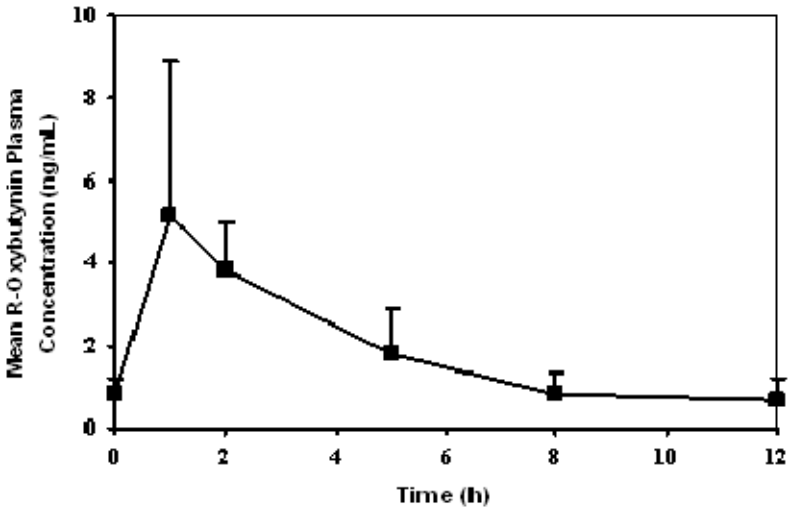
All Available Data Normalized to an Equivalent of DITROPAN Tablets 5 mg BID or TID at Steady State

	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

†$AUC_{0\text{-end of dosing interval}}$

Figure 2. Mean steady-state (±SD) R-oxybutynin plasma concentrations following administration of total daily DITROPAN Tablet dose of 7.5 mg to 15 mg (0.22 mg/kg to 0.53 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

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.

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.

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® (oxybutynin chloride) 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.

WARNINGS

Angioedema of the face, lips, tongue and/or larynx has been reported with oxybutynin. In some cases, angioedema occurred after the first dose. Angioedema

associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, oxybutynin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

PRECAUTIONS

Central Nervous System Effects

Oxybutynin is associated with anticholinergic central nervous system (CNS) effects (See **ADVERSE REACTIONS**). A variety of CNS anticholinergic effects have been reported, including hallucinations, agitation, confusion and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly in the first few months after beginning treatment or increasing the dose. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

DITROPAN should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms.

General

DITROPAN® (oxybutynin chloride) 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 oxybutynin may produce angioedema that could result in life-threatening airway obstruction. Patients should be advised to promptly discontinue oxybutynin therapy and seek immediate medical attention if they experience edema of the tongue, edema of the laryngopharynx, or difficulty breathing.

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.

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 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.

Pediatric Use

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

The safety and efficacy of DITROPAN Tablets were studied in 30 children 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 H_20 to 33 cm H_20, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H_20) from 39% to 20%.

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 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. 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 investigators 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)
Infections and Infestations	Urinary tract infection	6.5%
Psychiatric Disorders	Insomnia	5.5%
	Nervousness	6.5%
Nervous System Disorders	Dizziness	16.6%
	Somnolence	14.0%
	Headache	7.5%
Eye Disorders	Blurred vision	9.6%
Gastrointestinal Disorders	Dry mouth	71.4%
	Constipation	15.1%
	Nausea	11.6%
	Dyspepsia	6.0%
Renal and Urinary Disorders	Urinary Hesitation	8.5%
	Urinary Retention	6.0%

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 1 to <5% of patients using DITROPAN (5-20 mg/day) in all studies. *Infections and Infestations*: nasopharyngitis, upper respiratory tract infection, bronchitis, cystitis, fungal infection; *Metabolism and Nutrition Disorders*: fluid retention; *Psychiatric Disorders*: confusional state; *Nervous System Disorders*: dysgeusia, sinus headache; *Eye Disorders*: keratoconjunctivitis sicca, eye irritation; *Cardiac Disorders*: palpitations, sinus arrhythmia; *Vascular Disorders*: flushing; *Respiratory, Thoracic and Mediastinal Disorders*: nasal dryness, cough, pharyngolaryngeal pain, dry throat, sinus congestion, hoarseness, asthma, nasal congestion; *Gastrointestinal Disorders*: diarrhea, abdominal pain, loose stools, flatulence, vomiting, abdominal pain upper, dysphagia, aptyalism, eructation, tongue coated; *Skin and Subcutaneous Tissue Disorders*: dry skin, pruritis; *Musculoskeletal and Connective Tissue Disorders*: back pain, arthralgia, pain in extremity, flank pain; *Renal and Urinary Disorders*: dysuria, pollakiuria; *General Disorders and Administration Site Conditions*: fatigue, edema peripheral, asthenia, pain, thirst, edema; *Investigations*: blood pressure increased, blood glucose increased, blood pressure decreased; *Injury, Poisoning, and Procedural Complications*: fall.

Postmarketing Surveillance

Because postmarketing adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse events have been reported from worldwide postmarketing experience with

DITROPAN: *Psychiatric Disorders*: psychotic disorder, agitation, hallucination, memory impairment; *Nervous System Disorders*: convulsions; *Eye Disorders*: cycloplegia, mydriasis; *Cardiac Disorders*: tachycardia, QT interval prolongation; *Gastrointestinal Disorders*: decreased gastrointestinal motility; *Skin and Subcutaneous Tissue Disorders*: rash, decreased sweating; *Renal and Urinary Disorders*: impotence; *Reproductive System and Breast Disorders*: Suppression of lactation; *General Disorders and Administration Site Conditions:* hypersensitivity reactions, including angioedema with airway obstruction, urticaria, and face edema; rare anaphylactic reactions requiring hospitalization for emergency treatment.

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

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.

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.

Pharmacist: Dispense in tight, light-resistant container as defined in the USP.

Store at controlled room temperature 59-86°F (15-30°C).

REFERENCES

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

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.

Manufactured by sanofi-aventis U.S. LLC, Kansas City, MO 64137.

Marketed by Ortho Women's Health & Urology, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ 08869

(OMP Logo)

Revised December 2011