PRODUCT MONOGRAPH

pms-OXYBUTYNIN

(Oxybutynin Chloride Syrup and Tablets, USP)

1 mg/mL Syrup

2.5mg & 5mg Tablets

Anticholinergic/Antispasmodic Agent

Pharmascience Inc.
6111 Royalmount Avenue
Suite #100
Montreal, CANADA
H4P 2T4

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NAME OF DRUG

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THERAPUETIC CLASSIFICATION

Anticholinergic / Antispasmodic Agent

ACTION AND CLINICAL PHARMACOLOGY

pms-OXYBUTYNIN (Oxybutynin chloride) is a tertiary amine anticholinergic agent which exerts antimuscarinic as well as direct antispasmodic action on smooth muscle. In vitro studies have shown that its anticholinergic effects are weaker than those of atropine, but it possesses greater antispasmodic activity. No blocking effects occur at skeletal neuromuscular junctions or in autonomic ganglia (no antinicotinic effects).

In addition to its smooth muscle relaxing effects, oxybutynin exerts an analgesic and a local anesthetic effect. In animal studies the central nervous system and cardiovascular actions of oxybutynin were shown to be similar to but weaker than those of atropine.

Oxybutynin relaxes bladder smooth muscle. In patients with uninhibited neurogenic and reflex neurogenic bladder, 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. These effects are more consistently improved in patients with uninhibited neurogenic bladder.

Oxybutynin chloride is readily absorbed from the gastro-intestinal tract. The onset of action is approximately one hour after an oral dose and its duration 6 to 10 hours.

A single blind, single dose, randomized, cross-over study was carried out to evaluate the rate and extent of absorption and bioequivalence between pms-Oxybutynin 5 mg Syrup (test product) and Ditropan 5 mg Syrup, a Canadian marketed formulation (reference product). Bioequivalence between formulations was evaluated based on statistical comparaison of areas under the plasma concentrations versus time curves (AUC's), peak concentrations (C_{max}) and time to reach concentrations (T_{max}).

The summary of the results obtained is as follows:

Pharmacokinetic Results: Mean values (± CV%) were as follows:

	Oxybutynin-Reference	Oxybutynin-Test
Observed Tmax	0.8 (51.8)	0.7 (27.7)
Observed C_{max}	11.7 (68.8)	10.1 (58.4)
AUC_{cum}	19.35 (62.9)	17.01 (58.1)
AUC_{∞}	23.79 (50.1)	21.24 (51.2)
Ratio AUC_{cum} /AUC_{∞}	81.3 (19.1)	82.9 (16.4)
Mean Residence Time	1.4 (36.7)	1.4 (33.5)
Elimination T½	1.9 (50.7)	1.7 (56.5)
		.
	Metabolite-Reference	Metabolite-Test
Observed Tmax	0.9 (39.7)	0.9 (27.4)
Observed Cmax	5.5 (33.7)	5.1 (28.2)
AUC_{cum}	16.0 (34.4)	14.8 (32.5)
AUC_{∞}	17.7 (38.5)	16.3 (37.7)
Ratio AUC_{cum} /AUC_{∞}	91.4 (5.7)	92.1 (5.1)
Mean Residence Time	2.6 (9.4)	2.5 (9.1)
Elimination T½		2.0 (24.7)

The results of the present investigation show that no statistical difference could be detected for all the pharmacokinetic parameters under study. They also show that the test formulation,

pms-OXYBUTYNIN 5 mg tablet, is bioequivalent to the marketed Canadian formulation, DITROPAN 5 mg tablet, with a relative bioavailability of about 90%. The results of the tablet bioavalability study are as follows:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

for pms-OXYBUTYNIN 5mg Tablets (Pharmascience Inc., Québec, Canada, Lot #P-0008)

versus

DITROPAN 5mg Tablets (Procter & Gamble Pharmaceuticals Canada Inc., Ontario, Canada, Lot #K33838)

A 10 mg (2 x 5mg tablets) single oral administration in the fasting state

Measured Data of Oxybutynin

Parameter	Geometric Mean Arithmetic Mean (C.V.%)		Ratio of Geometric Mean
	Test	**Reference**	
AUC_T (ng.h/mL)	17.42 20.79 (62.3)	18.37 22.43 (72.2)	95
AUC∞ (ng.h/mL)	19.32 22.45 (58.0)	20.51 24.44 (68.0)	94
C_{max} (ng/mL)	9.58 11.53 (63.0)	10.03 12.35 (65.3)	96
T_{max} (h)	0.67 (39.1)	0.76 (35.8)	---
$T½_{el}$ (h)	1.77 (32.6)	2.03 (53.2)	---

For T_{max} and $T½_{el}$, the arithmetic mean only is presented.

STATISTICAL ANALYSIS

PARAMETER	POTENCY CORRECTED		POTENCY UNCORRECTED	
	RATIO(%)*	90%CI	RATIO (%)*	90% CI
AUC_T (T/R)**	100	89 - 111	95	85 – 106
AUC_∞ (T/R)	99	89 - 110	94	85 – 105
C_{max} (T/R)	100	---	96	---

* Based on the geometric mean ** Test/Reference

INDICATIONS AND CLINICAL USE

pms-OXYBUTYNIN (oxybutynin chloride) is indicated for the relief of symptoms associated with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria).

CONTRAINDICATIONS

pms-OXYBUTYNIN is contraindicated in patients with glaucoma, partial or complete obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony of the elderly or debilitated patient, megacolon, toxic megacolon complicating ulcerative colitis, severe colitis, myasthenia gravis, obstructive uropathy, and when the patient has an unstable cardiovascular status in acute hemorrhage. pms-OXYBUTYNIN is contraindicated in patients who have demonstrated hypersensitivity to the product.

WARNINGS

pms-OXYBUTYNIN , when administered in the presence of high environmental temperature, can cause heat prostration (fever and heat stroke due to decreased sweating).

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

Oxybutynin may produce drowsiness or blurred vision. The patient should be cautioned regarding activities requiring mental alertness, such as operating a motor vehicle or other machinery or performing hazardous work while taking this drug. Alcohol or other sedative drugs may enhance the drowsiness caused by pms-OXYBUTYNIN.

Pretreatment examination should include cystometry, and other appropriate diagnostic procedures. Cystometry should be repeated at appropriate intervals to evaluate response to therapy. The appropriate antimicrobial therapy should be instituted in the presence of infection.

PRECAUTIONS

pms-OXYBUTYNIN should be used with caution in the elderly and in patients with autonomic neuropathy, hepatic or renal disease. Administration of oxybutynin in large doses to patients with ulcerative colitis may suppress intestinal motility to the point of producing a paralytic ileus and precipitate or aggravate toxic megacolon, a serious complication of the disease.

The symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy may be aggravated following administration of the drug. pms-OXYBUTYNIN should be administered with caution to patients with hiatal hernia associated with reflux esophagitis, since anticholinergic drugs may aggravate this condition.

Use In Pregnancy

The safety of oxybutynin in pregnancy has not been established. Therefore, the drug should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefit to the patient outweighs the possible risk to the fetus.

Use In Children

Because the safety of oxybutynin in children under the age of five has not been established, use of the drug in this age group is not recommended.

Use In 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 the drug is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions have been reported with oxybutynin administration: dry mouth and throat, difficulty swallowing, decreased sweating , urinary hesitance and retention, blurred vision, dilation of the pupil, cycloplegia, increased ocular tension, palpitations, tachycardia, chest pain, syncope, flushing, nose bleed, drowsiness, weakness, dizziness, headache, insomnia, mood changes, nausea, vomiting, anorexia, metallic taste, constipation, bloated feeling, edema, impotence, suppression of lactation, interference with normal heat regulation, severe allergic reactions or drug idiosyncrasies including urticaria and other dermal manifestations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The symptoms of overdosage with oxybutynin may be any of those seen with other anticholinergic agents.

Symptoms may include signs of CNS excitation (eg., restlessness, tremor, irritability, delirium, hallucinations), flushing, fever, nausea, vomiting, tachycardia, hypotension or hypertension, respiratory failure, paralysis and coma.

In the event of an overdose or exaggerated response, tretment should be symptomatic and supportive. Induce emesis or perform gastric lavage (emesis is contraindicated in precomatose, convulsive, or psychotic state) and maintain respiration. Activated charcoal may be administered as well as magnesium sulphate. Physostigmine may be considered to reverse symptoms of anticholinergic intoxication.

Hyperpyrexia may be treated symptomatically with ice bags or other cold applications and alcohol sponges.

DOSAGE AND ADMINISTRATION

Adults:

The usual dose is 5 mg, two or three times a day. The maximum recommended dose is 5 mg, four times a day.

In elderly and debilitated patients, it is advisable to initiate treatment at the lowest recommended dosage and to increase the dosage carefully according to tolerance and response.

Children over 5 years of age:

The usual dose is 5 mg, two times a day. The maximum recommended dose is 5 mg, three times a day.

PHARMACEUTICAL INFORMATION

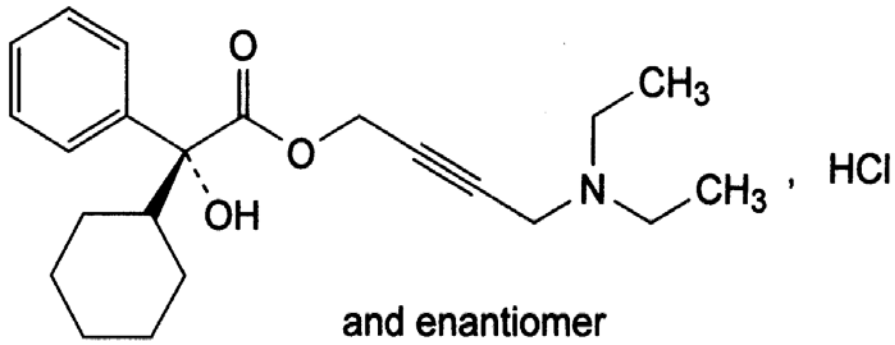
Drug Substance

Proper Name: Oxybutynin Chloride

Chemical Name

(±) α-Cyclohexyl-α-hydroxy-benzeneacetic acid 4-(diethylamino)-2-butynyl ester hydrochloride;
(±) α-phenylcyclohexaneglycolic acid 4-(diethylamino)-2-butynyl ester hydrochloride.

Structural Formula:



Molecular Formula: $C_{22}H_{31}NO_3 \cdot HCl$

Molecular Weight: 393.95

Description: Oxybutynin Chloride is a white crystalline solid, readily soluble in water and acids, but relatively insoluble in alkalis. The drug has a pKa of 6.96 and the melting point is 124°-129°C.

Composition:

pms-OXYBUTYNIN Syrup 1mg/mL:

contains 1 mg of oxybutynin chloride and the following nonmedicinal ingredients: Artificial Strawberry Flavour, Citric Acid, FD&C Green #3, Glycerin, Methylparaben, Sorbitol, Sucrose. Sodium Hydroxide is used for adjustment of pH.

pms-OXYBUTYNIN 2.5 mg Tablets:

Contains 2.5 mg of oxybutynin chloride and the following non-medicinal ingredients: lactose anhydrous, microcrystalline cellulose, and calcium stearate.

pms-OXYBUTYNIN 5 mg Tablets:
Contains 5 mg of oxybutynin chloride and the following non-medicinal ingredients: lactose anhydrous, microcrystalline cellulose, calcium stearate, and FD&C Blue #1 Aluminum Lake 13%.

Stability and Storage Recommendations:
Store at room temperature (15°- 30°C) in tight container. Protect from light.

AVAILABILITY OF DOSAGE FORMS

pms-OXYBUTYNIN Syrup 1mg/mL is a clear liquid with a greenish colour. It is available in HDPE and amber PET bottles of 500 mL.

pms-OXYBUTYNIN 2.5mg Tablets are white, round, biconvex « 7/32 » tablets debossed **"P "** logo on one side and **"2.5"** on the other side. Available in HDPE bottles of 100 and in blister pack boxes of 30 (3 x 10 tablets).

pms-OXYBUTYNIN 5mg Tablets are "5/16" round blue, tablets debossed **"oxy" over "5" on the scored side and "P Logo" on the other side**. Available in HDPE bottles of 100 and 500 and in blister pack boxes of 30 (3 x 10 tablets).

PHARMACOLOGY

In a series of in vitro tests, oxybutynin chloride was found to be more effective than propantheline, methantheline and atropine in inhibiting barium chloride-induced contractions in rabbit bladder detrusor muscle. It was however, less active than the other drugs in inhibiting contractions caused by histamine and carbamylcholine.

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

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

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

Oxybutynin chloride was less potent than atropine but similar in potency to methscopolamine in producing characteristic anticholingergic CNS effect in dogs.

The cardiovascular actions of oxybutynin chloride in the anesthetized dog were also relatively weak.

TOXICOLOGY

Acute Toxicity :

Compound	Species	Route	LD_{50}(') mg/kg	TD_{30}(') mg/kg
Oxybutynin	Mouse " "	Oral I.V. I.P.	725 (557-942) 68 (64-73) 185 (153-224)	16.4 (12-23) 3.4 (2.8-4.1) 13 (10.4-16.3)
	Rat	Oral	2030 (1573-2619)	45.0 (29.69)
	Dog "	Oral S.C. I.V.	>400	5.6 11.0 1.0

Approximate Minimum Lethal Dose:

Dog I.V. > 25 but < 50 mg/kg

Dog P.O. > 750 but <1000 mg/kg

*95% confidence limits

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

Subacute and Chronic Toxicity:

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

In a six month rat study, 20-200 mg/kg/day p.o. was administered 6 days per week. At the lowest dose no significant toxic effects were observed, while rats receiving 63-200 mg/kg/day showed signs of continuous acute pharmacologic effects, decreased food consumption with

suppression of weight gain, and somewhat dose-related pathological changes consisting primarily or irregular and enlarged hepatic cells and of degenerative changes in kidney tubules.

Rats receiving 20 mg/kg/day or some 80-130 times the EHDD of oxybutynin showed no significant toxic effects as measured by growth, appearance, and hematology. At necropsy no significant gross pathological changes attributable to the drug could be found, nor were any drug-related lesions noted upon histopathologic examination.

Rats receiving 250 - 1300 times the EHDD, or 63 - 200 mg/kg/day, showed: (a) continuous acute pharmacologic effects from daily administration of oxybutynin, (b) decreased food consumption and corresponding suppression of weight gain, (c) pathological changes consisting primarily of irregular and enlarged hepatic cells and degenerative changes in kidney tubules. Pathological changes were somewhat dose related but, nevertheless, minor in the opinion of the pathologist. No hematologic changes were observed.

A six month study in dogs showed no toxic effects following administration of 3 and 6 mg/kg/day of oxybutynin chloride 6 days per week, while higher doses 48-80 times fo the EHDD produced anorexia, tremors and nervousness during the first 4 weeks of the study. These signs of toxicity diminished during the remainder of the study and no other abnormalities were observed.

REPRODUCTIVE AND FETAL DEVELOPMENT

There were no abnormalities noted in the 126 young born to pregnant mice which had received large doses of oxybutynin during critical days of pregnancy. Further these young developed normally during the 3-week postnatal period to weanling age, and demonstrated a normal rate of

survival.

From the hamsters treated with oxybutynin 96 viable fetuses were delivered. None of these exhibited any abnormalities. The incidence of dead and undeveloped fetuses in the treated group was no greater than in a control group. Forty-four normal developed fetuses were produced by the treated rabbits, and one was found with a cleft palate. Cleft palates are also seen with similar incidence in control populations.

Female rats given oxybutynin prior to and throughout mating, gestation, and lactation produced litters of normal weight, size, and appearance. The offspring of the treated group exhibited postnatal growth and survival to weaning which were not different from the growth and survival of control pups. Of the 144 live newborn rats produced by the treated females, none had any observable abnormalities.

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