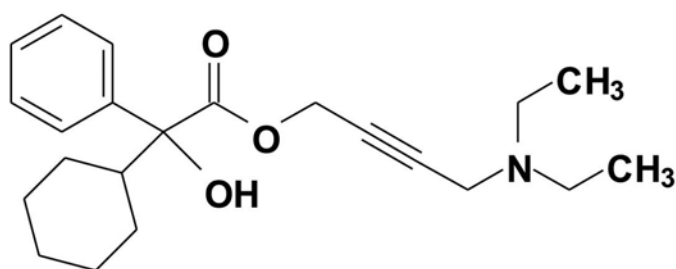


OXYTROL[®] TRANSDERMAL DRUG DELIVERY SYSTEM**NAME OF THE MEDICINE**

Oxybutynin

The structure of oxybutynin 4-(diethylamino)but-2-ynyl (RS)-2-cyclohexyl-2-hydroxy-2-phenylacetate is given below. Oxybutynin is an antispasmodic, anticholinergic agent, and is administered as a racemate of R- and S-isomers. The molecular weight of the compound is 357.49 and the CAS number is 5633-20-5. Oxybutynin is a white powder, soluble in alcohol, but relatively insoluble in water.

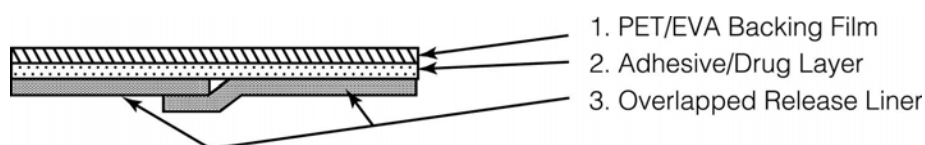
**DESCRIPTION**

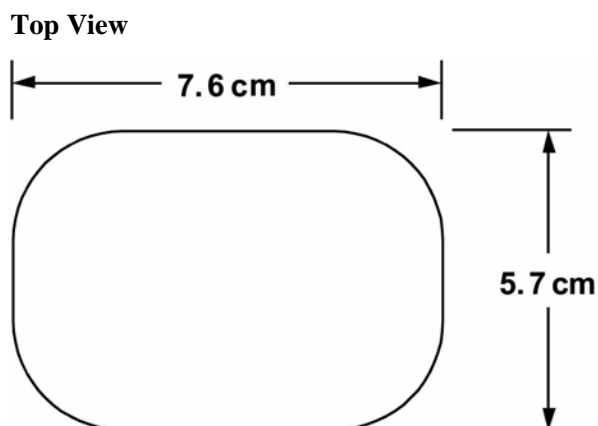
Oxytrol[®] is a transdermal drug delivery system designed to deliver oxybutynin continuously and consistently over a 3 to 4 day interval after application on to intact skin. Oxytrol[®] is available as a 39 cm² patch containing 36 mg of oxybutynin. Oxytrol[®] has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day.

Transdermal Patch Components

Oxytrol[®] is a matrix-type transdermal patch composed of three layers as illustrated in Figure 1 below. Layer 1 (Backing Film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix patch with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 (Adhesive/Drug Layer) is a cast film of acrylic adhesive containing oxybutynin and glycerol triacetate. Layer 3 (Release Liner) is two overlapped siliconized polyester strips that are peeled off and discarded by the patient prior to applying the matrix patch.

Figure 1: Side and top views of Oxytrol[®]. (Not to scale)

Side View



PHARMACOLOGY

The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride. Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with conditions characterised by involuntary detrusor contractions, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction. Oxybutynin thus decreases urinary urgency and the frequency of both incontinence episodes and voluntary urination.

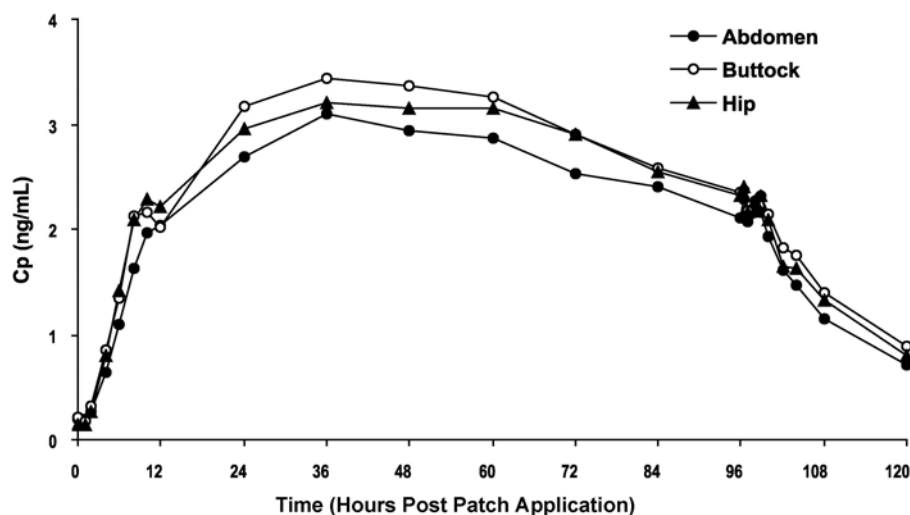
Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly in the R-isomer. The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Oxybutynin is absorbed through the skin and into the systemic circulation by passive diffusion across the stratum corneum. The average daily dose of oxybutynin absorbed from the 39 cm² Oxytrol[®] patch is 3.9 mg. The average (SD) nominal dose, 0.10 (0.02) mg oxybutynin per cm² surface area, was obtained from analysis of residual oxybutynin content of patches worn over a continuous 4-day period during 303 separate occasions in 76 healthy volunteers. Following application of the first Oxytrol[®] 3.9 mg/day transdermal patch, oxybutynin plasma concentration increases for approximately 24 to 48 hours, reaching average maximum concentrations of 3 to 4 ng/mL. Thereafter, steady concentrations are maintained for up to 96 hours. Absorption of oxybutynin is bioequivalent when Oxytrol[®] is applied to the abdomen, buttocks, or hip. Average plasma concentrations measured during a randomised, crossover study of the three recommended application sites in 24 healthy men and women are shown in Figure 2.

Figure 2: Average plasma oxybutynin concentrations (Cp) in 24 healthy male and female volunteers during single-dose application of 39 cm² Oxytrol[®] patch (3.9 mg/day) to the abdomen, buttock, and hip (patch removal at 96 hours).



Steady-state conditions are reached during the second Oxytrol[®] application. Average steady-state plasma concentrations were 3.1 ng/mL for oxybutynin and 3.8 ng/mL for N-desethyloxybutynin (Figure 3). Table 1 provides a summary of pharmacokinetic parameters of oxybutynin in healthy volunteers after single and multiple applications of Oxytrol[®].

Figure 3: Average (SEM) steady-state oxybutynin and N-desethyloxybutynin plasma concentrations (Cp) measured in 13 healthy volunteers following the second 39 cm² Oxytrol[®] patch (3.9 mg/day) application in a multiple-dose, randomised, crossover study.

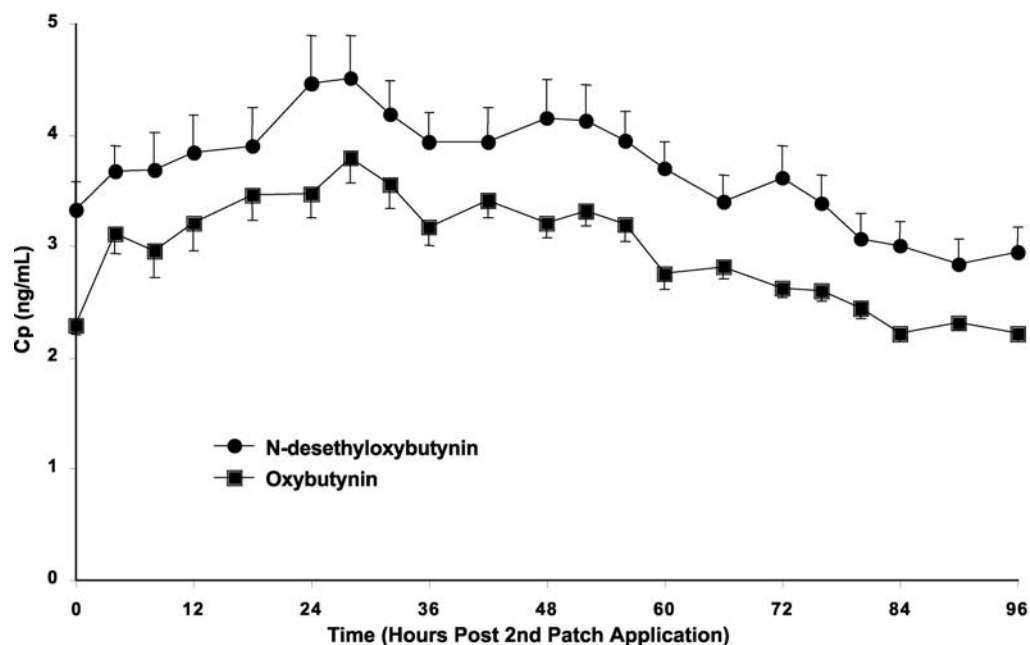


Table 1: Mean (SD) oxybutynin pharmacokinetic parameters from single and multiple dose studies in healthy men and women volunteers after application of Oxytrol[®] on the abdomen.

Dosing	Oxybutynin			
	C _{max} (SD) (ng/mL)	T _{max} ¹ (hr)	C _{avg} (SD) (ng/mL)	AUC (SD) (ng/mL x hr)
Single	3.0 (0.8)	48	—	245 (59) ²
	3.4 (1.1)	36	—	279 (99) ²
Multiple	6.6 (2.4)	10	4.2 (1.1)	408 (108) ³
	4.2 (1.0)	28	3.1 (0.7)	259 (57) ⁴

¹ T_{max} given as median² AUC_{inf}³ AUC₀₋₉₆⁴ AUC₀₋₈₄***Distribution***

Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 L after intravenous administration of 5 mg oxybutynin chloride.

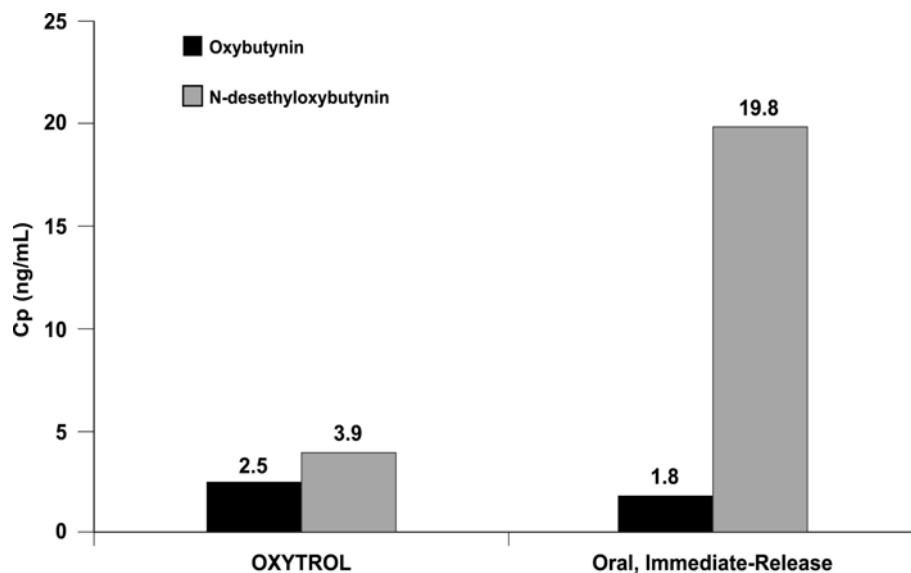
Metabolism

Oxybutynin is metabolised primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and N-desethyloxybutynin, which is pharmacologically active.

After oral administration of oxybutynin, pre-systemic first-pass metabolism results in an oral bioavailability of approximately 6% and higher plasma concentration of the N-desethyl metabolite compared to oxybutynin (see Figure 4). The plasma concentration AUC ratio of N-desethyl metabolite to parent compound following a single 5 mg oral dose of oxybutynin chloride was 11.9:1.

Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism, reducing the formation of the N-desethyl metabolite (see Figure 4). Only small amounts of CYP3A4 are found in skin, limiting pre-systemic metabolism during transdermal absorption. The resulting plasma concentration AUC ratio of N-desethyl metabolite to parent compound following multiple Oxytrol[®] applications was 1.3:1.

Figure 4: Average plasma concentrations (C_p) measured after a single, 96-hour application of the 39 cm² Oxytrol[®] patch (3.9 mg/day) (AUC_{inf}/96) and a single, 5 mg, oral immediate-release dose of oxybutynin chloride (AUC_{inf}/8) in 16 healthy male and female volunteers.



Following intravenous administration, the elimination half-life of oxybutynin is approximately 2 hours. Following removal of Oxytrol[®], plasma concentrations of oxybutynin and N-desethyloxybutynin decline with an apparent half-life of approximately 7 to 8 hours.

Excretion

Oxybutynin is extensively metabolised 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 N-desethyloxybutynin.

Special Populations

Geriatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were similar in all patients studied.

Paediatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were not evaluated in individuals younger than 18 years of age. See **PRECAUTIONS: Paediatric Use**.

Gender: There were no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following application of Oxytrol[®].

Race: Available data suggest that there are no significant differences in the pharmacokinetics of oxybutynin based on race in healthy volunteers following administration of Oxytrol[®]. Japanese volunteers demonstrated a somewhat lower metabolism of oxybutynin to N-desethyloxybutynin compared to Caucasian volunteers.

Renal Insufficiency: There is no experience with the use of Oxytrol[®] in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of Oxytrol[®] in patients with hepatic insufficiency.

Interactions with other medicines: See **PRECAUTIONS: Interactions with other medicines**.

Adhesion

Adhesion was periodically evaluated during the Phase 3 studies. Of the 4,746 Oxytrol[®] evaluations in the Phase 3 trials, 20 (0.4%) were observed at clinic visits to have become completely detached and 35 (0.7%) became partially detached during routine clinic use. Similar to the pharmacokinetic studies, > 98% of the

patches evaluated in the Phase 3 studies were assessed as being $\geq 75\%$ attached and thus would be expected to perform as anticipated.

CLINICAL TRIALS

The efficacy and safety of Oxytrol[®] were evaluated in patients with urge urinary incontinence in two Phase 3 controlled studies and one open-label extension. Study 1 was a Phase 3, placebo controlled study, comparing the safety and efficacy of 13 cm², 26 cm² and 39 cm² Oxytrol[®] at dose levels of 1.3, 2.6, and 3.9 mg/day to placebo in 520 patients. Open-label treatment was available for patients completing the study. Study 2 was a Phase 3 study, comparing the safety and efficacy of 39cm² Oxytrol[®] 3.9 mg/day versus active and placebo controls in 361 patients.

Study 1 was a randomised, double-blind, placebo-controlled, parallel group study of three dose levels of Oxytrol[®] conducted in 520 patients. The 12-week double-blind treatment included Oxytrol[®] doses of 1.3, 2.6, and 3.9 mg/day with matching placebo. An open-label, dose titration treatment extension allowed continued treatment for up to an additional 40 weeks for patients completing the double-blind period. The majority of patients were Caucasian (91%) and female (92%) with a mean age of 61 years (range, 20 to 88 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge), urge incontinence episodes of ≥ 10 per week, and ≥ 8 micturitions per day. The patient's medical history and a urinary diary during the treatment-free baseline period confirmed the diagnosis of urge incontinence. Approximately 80% of patients had no prior pharmacological treatment for incontinence. Reductions in weekly incontinence episodes, urinary frequency, and urinary void volume between placebo and active treatment groups are summarised in Table 2.

Table 2: Mean and median change from baseline to end of treatment (Week 12 or last observation carried forward) in incontinence episodes, urinary frequency, and urinary void volume in patients treated with Oxytrol[®] 3.9 mg/day or placebo for 12 weeks (Study 1).

Parameter	Placebo (N=127)		OXYTROL [®] 3.9 mg/day (N=120)	
	Mean (SD)	Median	Mean (SD)	Median
Weekly Incontinence Episodes				
Baseline	37.7 (24.0)	30	34.3 (18.2)	31
Reduction	19.2 (21.4)	15	21.0 (17.1)	19
p value vs. placebo	—		0.0265*	
Daily Urinary Frequency				
Baseline	12.3 (3.5)	11	11.8 (3.1)	11
Reduction	1.6 (3.0)	1	2.2 (2.5)	2
p value vs. placebo	—		0.0313*	
Urinary Void Volume (mL)				
Baseline	175.9 (69.5)	166.5	171.6 (65.1)	168
Increase	10.5 (56.9)	5.5	31.6 (65.6)	26
p value vs. placebo	—		0.0009**	

*Comparison significant if $p < 0.05$

**Comparison significant if $p \leq 0.0167$

Study 2 was a randomised, double-blind, double-dummy, study of Oxytrol[®] 3.9 mg/day versus active and placebo controls conducted in 361 patients. The 12-week double-blind treatment included an Oxytrol[®] dose of 3.9 mg/day, an active comparator, and placebo. The study was to test superiority over placebo and equivalence with tolterodine. Equivalence to tolterodine was determined by calculating the 95% confidence interval (CI) for the difference in least squares adjusted means from the ANCOVA model for change in number of incontinence episodes per day, i.e. -1.5 to +1.5. The majority of patients were Caucasian (95%) and female (93%) with a mean age of 64 years (range, 18 to 89 years). Entry criteria required that all patients have urge or mixed incontinence (with a predominance of urge) and had achieved a beneficial response from the anticholinergic treatment they were using at the time of study entry. The average duration of prior pharmacological treatment was greater than 2 years. The patient's medical history and a urinary diary during the treatment-free baseline period confirmed the diagnosis of urge incontinence. Reductions in daily incontinence episodes, urinary frequency, and urinary void volume between placebo and active treatment groups are summarised in Table 3.

Table 3: Mean and median change from baseline to end of treatment (Week 12 or last observation carried forward) in incontinence episodes, urinary frequency, and urinary void volume in patients treated with Oxytrol[®] 3.9 mg/day or placebo orally once daily or tolterodine long acting capsules 4 mg orally once daily for 12 weeks (Study 2).

Parameter	Placebo** (N=117)		Oxytrol [®] 3.9 mg/day** (N=121)		Tolterodine** (N=123)	
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
Daily Incontinence Episodes						
Baseline	5.0 (3.2)	4	4.7 (2.9)	4	5 (2.9)	4
Reduction	2.1 (3.0)	2	2.9 (3.0)	3	3.2 (2.8)	3
p value vs. placebo	—		0.0137*		0.0011*	
Daily Urinary Frequency						
Baseline	12.3 (3.3)	12	12.4 (2.9)	12	12.1 (3.3)	12
Reduction	1.4 (2.7)	1	1.9 (2.7)	2	2.2 (2.6)	2
p value vs. placebo	—		0.1010*		0.0025*	
Urinary Void Volume (mL)						
Baseline	175.0 (68.0)	171.0	164.8 (62.3)	160	165.2 (61.1)	150
Increase	9.3 (63.1)	5.5	32.0 (55.2)	24	29.3 (56.9)	29
p value vs. placebo	—		0.0010*		0.0017*	

*Comparison significant if $p < 0.05$

** 95% CI around the difference in number of incontinence episodes per day for oxybutynin versus tolterodine was [-1.0, 0.0]. Both actives, oxybutynin and tolterodine, were statistically superior to placebo and equivalent to each other.

INDICATIONS

Oxytrol[®] is indicated for the treatment of overactive bladder with symptoms of urinary frequency, urgency or incontinence or any combination of these symptoms.

CONTRAINDICATIONS

Oxytrol[®] is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, severe ulcerative colitis, toxic megacolon and myasthenia gravis.

Oxytrol[®] is also contraindicated in patients who have demonstrated hypersensitivity to oxybutynin or other components of the product.

PRECAUTIONS

Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Oxytrol[®]. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Oxytrol[®] should be used with caution in patients with hepatic or renal impairment.

Anticholinergic medicinal products should be used with caution in patients who have autonomic neuropathy, cognitive impairment or Parkinson's disease.

Oxytrol[®] may exacerbate the symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, cardiac arrhythmias, tachycardia, hypertension and prostatic hypertrophy.

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

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

Oxytrol[®], like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis and intestinal atony (See **CONTRAINDICATIONS**). Oxytrol[®] should be used with caution in patients who have gastro-oesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate oesophagitis. Diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance, treatment with Oxytrol[®] would be inappropriate and possibly harmful.

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 are used in a hot environment. 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 using Oxytrol[®] should exercise caution when driving or operating machinery.

Oxytrol[®] should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new patch to avoid re-application to the same site within 7 days. Details on use of the patch are explained in the pack insert that should be dispensed with the product.

Effects on fertility

Reproduction studies with oxybutynin hydrochloride in the rat showed no definite evidence of impaired fertility.

Use in Pregnancy***Pregnancy Category B1***

Animal studies with oxybutynin showed no clear evidence of teratogenicity or other embryotoxic effects in rats and rabbits at oral doses up to 160 and 100 mg/kg/day respectively. The incidence of abortion was slightly increased at the highest dose level in rabbits.

The safety of oxybutynin hydrochloride in women who are or who may become pregnant has not been established; it should be given only when the potential benefits outweigh the possible hazards.

Australian categorisation definition of:

Category B1:

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

Use in Lactation

There is some evidence from animal studies that oxybutynin or its metabolites are excreted in milk. It is not known whether oxybutynin is excreted in human milk. Caution should be exercised when Oxytrol[®] is administered to a nursing woman.

Paediatric Use

The safety and efficacy of Oxytrol[®] in paediatric patients have not been established. However, the safety and efficacy of Ditropan (oxybutynin hydrochloride 5 mg tablet) administration have been demonstrated for children five years of age and older.

Use in the Elderly

Of the total number of patients in the clinical studies of Oxytrol[®] 49% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between elderly and younger patients.

Carcinogenicity

A 24-month study in rats at oral doses of oxybutynin hydrochloride of 20, 80 and 160 mg/kg/day showed no evidence of carcinogenicity. These doses are approximately 9, 36 and 72 times the maximum exposure in humans taking an oral dose based on body surface area.

Genotoxicity

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

Interactions with other medicines

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that produce dry mouth, constipation, somnolence, 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. Pharmacokinetic studies have not been performed with patients concomitantly receiving cytochrome P450 enzyme inhibitors, such as antimycotic agents (e.g. ketoconazole, itraconazole, and miconazole) or macrolide antibiotics (e.g. erythromycin and clarithromycin).

ADVERSE EFFECTS

The safety of Oxytrol[®] was evaluated in a total of 417 patients who participated in two Phase 3 clinical efficacy and safety studies and an open-label extension. Additional safety information was collected in Phase 1 and Phase 2 trials. In the two pivotal studies, a total of 246 patients received the 3.9 mg/day strength of Oxytrol[®] during the 12-week treatment periods. A total of 411 patients entered the open-label extension and

of those, 65 patients and 52 patients received Oxytrol[®] for at least 24 weeks and at least 36 weeks, respectively.

No deaths were reported during treatment. No serious adverse events related to treatment were reported. Adverse events reported in the pivotal trials are summarised in Tables 4 and 5 below.

Table 4: Number (%) of adverse events occurring in $\geq 2\%$ of Oxytrol[®]-treated patients and greater in Oxytrol[®] group than in placebo group (Study 1).

Adverse Event*	Placebo (N=132)		OXYTROL [®] (3.9 mg/day) (N=125)	
	N	%	N	%
Application site pruritus	8	6.1%	21	16.8%
Application site erythema	3	2.3%	7	5.6%
Application site vesicles	0	0.0%	4	3.2%
Dry mouth	11	8.3%	12	9.6%
Diarrhoea	3	2.3%	4	3.2%
Dysuria	0	0.0%	3	2.4%

*includes adverse events judged by the investigator as possibly, probably or definitely treatment-related.

Table 5: Number (%) of adverse events occurring in $\geq 2\%$ of Oxytrol[®]-treated patients and greater in Oxytrol[®] group than in placebo group (Study 2).

Adverse Event*	Placebo (N=117)		OXYTROL [®] (3.9 mg/day) (N=121)	
	N	%	N	%
Application site pruritus	5	4.3%	17	14.0%
Application site erythema	2	1.7%	10	8.3%
Application site rash	1	0.9%	4	3.3%
Application site macules	0	0.0%	3	2.5%
Dry mouth	2	1.7%	5	4.1%
Constipation	0	0.0%	4	3.3%
Abnormal vision	0	0.0%	3	2.5%

*includes adverse events judged by the investigator as possibly, probably or definitely treatment-related.

Other adverse events reported by $> 1\%$ of Oxytrol[®]-treated patients, and judged by the investigator to be possibly, probably or definitely related to treatment include: abdominal pain, nausea, flatulence, fatigue, somnolence, headache, flushing, rash, application site burning and back pain. Treatment-related adverse

events with an incidence of < 1% were abdominal pain, dysuria, somnolence, nausea, backpain, urinary tract infections, inflicted injury, rhinitis, palpitations and hot flushes.

Most treatment-related adverse events were described as mild or moderate in intensity. Severe application site reactions were reported by 6.4% of Oxytrol[®]-treated patients in Study 1 and by 5.0% of Oxytrol[®]-treated patients in Study 2.

Treatment-related adverse events that resulted in discontinuation were reported by 11.2% of Oxytrol[®]-treated patients in Study 1 and 10.7% of Oxytrol[®]-treated patients in Study 2. Most of these were secondary to application site reaction. In the two pivotal studies, no patient discontinued Oxytrol[®] treatment due to dry mouth. In the open-label extension, the most common treatment-related adverse events were: application site pruritus, application site erythema and dry mouth.

DOSAGE AND ADMINISTRATION

Oxytrol[®] should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new patch, avoid re-application to the same site within 7 days. The dose of Oxytrol[®] is one (3.9 mg/day) patch applied twice weekly (every 3 to 4 days).

OVERDOSAGE

Symptoms

Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention. Ingestion of 100 mg oral oxybutynin hydrochloride in association with alcohol has been reported in a 13 year old boy who experienced memory loss, and in 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 recovered fully with symptomatic treatment.

Treatment

Plasma concentration of oxybutynin declines within 1 to 2 hours after removal of transdermal patch(es). Patients should be monitored until symptoms resolve.

STORAGE

Store below 25°C (Do not refrigerate, do not freeze). Protect from moisture. Do not store outside the sealed pouch. Apply immediately after removal from the protective pouch. Discard used Oxytrol[®] by folding and disposing of the patches in household refuse in a manner that prevents accidental application or ingestion by children, pets, or others.

PRESENTATION

Oxytrol[®], Oxybutynin Transdermal Drug Delivery System 3.9 mg of oxybutynin per day.
8 patch pack (one month's treatment).
2 patch pack (not marketed).

NAME AND ADDRESS OF THE SPONSOR

Hospira NZ Limited
23 Haining Street
Te Aro
Wellington
New Zealand

CLASSIFICATION

Prescription Medicine

Date of Preparation: 12 March 2008.

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