

# **PRODUCT MONOGRAPH**

## **OXYTROL™**

**OXYBUTYNIN TRANSDERMAL SYSTEM**  
**Continuous Delivery for Twice Weekly Dosing**

**36 mg oxybutynin (3.9 mg / day system)**

**Antispasmodic / anticholinergic agent for treatment of overactive bladder**

**Watson Laboratories, Inc.**  
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**USA**

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## **PRODUCT MONOGRAPH**

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#### **OXYBUTYNIN TRANSDERMAL SYSTEM Continuous Delivery for Twice Weekly Dosing 36 mg oxybutynin (3.9 mg / day system)**

### **THERAPEUTIC CLASSIFICATION**

Antispasmodic / anticholinergic agent for treatment of overactive bladder

### **ACTIONS AND CLINICAL PHARMACOLOGY**

Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with overactive bladder, characterized by detrusor muscle instability or hyperreflexia, 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 R-isomer of oxybutynin shows greater selectivity for the M<sub>3</sub> and M<sub>1</sub> muscarinic subtypes (predominant in bladder detrusor muscle and parotid gland) compared to the M<sub>2</sub> subtype (predominant in cardiac tissue).

The active metabolite, N-desethoxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies.

**OXYTROL™** (oxybutynin transdermal system) is designed to deliver oxybutynin continuously and consistently over a 3 to 4-day time interval after application to intact skin. The **OXYTROL™** system has a skin contact surface area of 39 cm<sup>2</sup> and contains 36 mg of oxybutynin.

Oxybutynin is transported across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. The average daily dose of oxybutynin absorbed from the 39 cm<sup>2</sup> **OXYTROL™** system is 3.9 mg. The average (SD) nominal dose, 0.10 (0.02) mg oxybutynin per cm<sup>2</sup> surface area, was obtained from analysis of residual oxybutynin content of systems worn over a continuous 4-day interval during 303 separate occasions in 76 healthy volunteers. Following application of the first **OXYTROL™** 3.9 mg/day system, oxybutynin plasma concentrations increase 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. (See **PHARMACOLOGY, Pharmacokinetics**). Absorption of oxybutynin is bioequivalent when **OXYTROL™** is applied to the abdomen, buttocks or hip.

## INDICATIONS AND CLINICAL USE

**OXYTROL™** is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

## CONTRAINDICATIONS

**OXYTROL™** is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions.

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

## PRECAUTIONS

### *General:*

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.

***Hepatic or Renal Impairment:***

**OXYTROL™** should be used with caution in patients with hepatic or renal impairment.

***Urinary Retention:***

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

***Gastrointestinal Disorders:***

**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, intestinal atony, and myasthenia gravis.

**OXYTROL™** 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.

***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, but greater sensitivity of some older individuals cannot be ruled out.

***Use in Children:***

The safety and efficacy of **OXYTROL** in pediatric patients have not been established.

***Use in Pregnancy:***

The safety of **OXYTROL™** administration to women who are or who may become pregnant has not been established. Therefore, **OXYTROL™** 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 **OXYTROL™** is administered to a nursing woman.

***Dependence Liability:***

**OXYTROL™** (Oxybutynin Transdermal System) has a low potential for abuse.

Oxybutynin is an anticholinergic compound with a well known safety and efficacy profile. The compound does not possess characteristics commonly associated with drugs of dependence liability or abuse, such as those with euphoric, central nervous system (CNS) depressant, or stimulant action.

***Drug Interactions:***

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that 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.

Pharmacokinetic studies 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), have not been performed.

## ADVERSE REACTIONS

The safety of **OXYTROL™** was evaluated in a total of 417 patients who participated in two Phase III clinical efficacy and safety studies and an open-label extension. Additional safety information was collected in Phase I and Phase II trials. In the two pivotal studies, (Study 1 and Study 2; see Clinical Studies section of the Product Monograph), a total of 246 patients received **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 summarized in Tables 1 and 2 below.

**Table 1: 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
Dry mouth	11	8.3	12	9.6
Application site erythema	3	2.3	7	5.6
Application site vesicles	0	0.0	4	3.2
Diarrhea	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 2: 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
Dry mouth	2	1.7	5	4.1
Constipation	0	0.0	4	3.3
Application site rash	1	0.9	4	3.3
Application site macules	0	0.0	3	2.5
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.

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**<sup>™</sup> 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.

### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Overdosage using **OXYTROL**<sup>™</sup> (oxybutynin transdermal system) is unlikely. Each 39 cm<sup>2</sup> system contains 36 mg oxybutynin and delivers 3.9 mg/day when attached to the skin. Thus, 36 mg oxybutynin would be the maximum dose possible if a system were inadvertently taken internally. In terms of transdermal application, if an entire box of 24 systems were applied simultaneously and worn for 24 hours, the resulting dose would be 93.6 mg.

Case reports of oral overdose with oxybutynin chloride indicate that doses of this magnitude should resolve with withdrawal of exposure and supportive care. Overdose with oral 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 oral 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, following by disorientation and

agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients recovered fully with symptomatic treatment.

In the event of a possible overdose, the transdermal system(s) should be removed immediately and medical attention sought. Plasma concentrations of oxybutynin and N-desethyloxybutynin decline within 1 to 2 hours after removal of transdermal system(s). If an overdose is suspected, patients should be monitored until symptoms resolve.

## **DOSAGE AND ADMINISTRATION**

**OXYTROL™** (oxybutynin transdermal system) is designed to deliver oxybutynin continuously and consistently over a 3 to 4-day time interval after application to intact skin. The **OXYTROL™** system has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%) and contains 36 mg of oxybutynin.

**OXYTROL™** adheres well to the skin when applied according to instructions (see Administration below).

### **Usual Adult Dosage**

The recommended starting dose is one 3.9 mg/day system applied twice weekly (every 3 to 4 days).

**Administration**

**OXYTROL™** should be applied to dry, intact skin on the abdomen, hip or buttock.

Apply immediately after removal from the protective pouch. A new application site should be selected with each new **OXYTROL™** system to avoid re-application to the same site within 7 days.

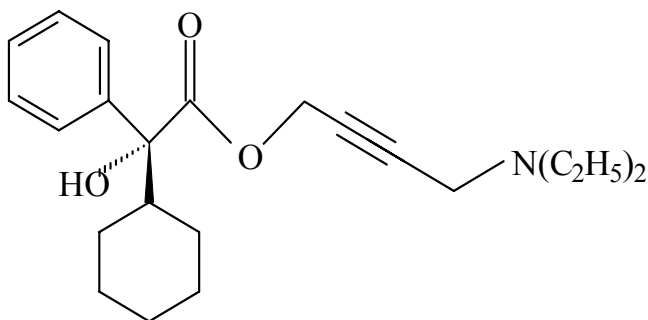
## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

**Proper name:** oxybutynin

**Chemical name:** d,l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate

**Structural formula:**



**Molecular formula:** C<sub>22</sub>H<sub>31</sub>NO<sub>3</sub>

**Molecular weight:** 357

**Description:** Oxybutynin is a white powder. It is soluble in alcohol, but relatively insoluble in water. Oxybutynin is administered as a racemate of R- and S-enantiomers.

The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride.

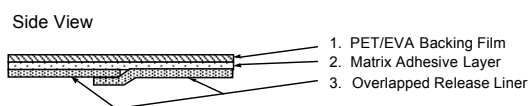
## COMPOSITION

### **OXYTROL™ 3.9 mg/day (oxybutynin transdermal system)**

Each 39 cm<sup>2</sup> system imprinted with “OXYTROL 3.9” contains 36 mg oxybutynin for nominal delivery of 3.9 mg oxybutynin per day when dosed in a twice weekly regimen.

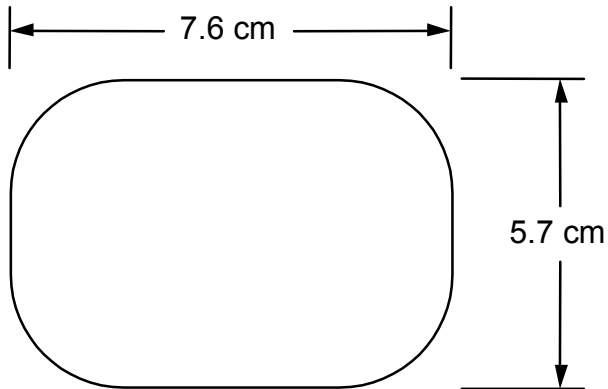
### **Transdermal System Components**

**OXYTROL™** is a matrix-type transdermal system composed of 3 layers, illustrated in the figure below. Layer 1 (Backing Film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix system 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 triacetin USP. Layer 3 (Release Liner) is two overlapped siliconized polyester strips that are peeled off and discarded by the patient prior to applying the matrix system.



Top View

39 cm<sup>2</sup> System Dimensions



### Storage

Store at room temperature at 15 - 30EC. Protect from moisture and humidity. Do not store outside the sealed pouch. Apply immediately after removal from protective pouch. Discard used **OXYTROL™** in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

### AVAILABILITY OF DOSAGE FORM

**OXYTROL™** (oxybutynin transdermal system) is supplied in Patient Calendar Boxes of 8 systems and 24 systems. **OXYTROL™** is also supplied in boxes of 8 systems for use as physician samples.

**INFORMATION FOR THE PATIENT****OXYTROL™  
OXYBUTYNIN TRANSDERMAL SYSTEM**

Read this information carefully before you begin treatment. Read the information whenever you get more medicine, there may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about OXYTROL, ask your doctor. Only your doctor can determine if OXYTROL is right for you.

**What is OXYTROL?**

OXYTROL is a transdermal system (skin patch) to treat overactive bladder. OXYTROL delivers the medicine slowly and constantly through your skin and into your bloodstream for the 3 or 4 days that you wear the patch.

Overactive bladder makes it hard to control when you urinate (pass water). Overactive bladder can make you urinate more often (increased frequency) or make you feel the need to urinate often (urgency). Overactive bladder can also lead to accidental urine loss (leaking or wetting oneself).

**What are the ingredients of OXYTROL?**

OXYTROL contains the same active medicinal ingredient (oxybutynin) as oxybutynin tablets and syrup. The oxybutynin in OXYTROL is dissolved in the thin layer of adhesive that sticks the patch to your skin. This layer contains acrylic adhesive and

triacetin in addition to the oxybutynin medicinal ingredient. A second layer, on top of the adhesive layer, is made of a polyester / ethylene-vinyl acetate film. This outer layer protects the adhesive drug layer from moisture and damage when you are wearing the patch. The unused Oxytrol System also contains a third layer made of siliconized polyester which you will peel off and discard before applying your patch.

**Who should NOT use OXYTROL?**

Do NOT use OXYTROL if you have the following medical conditions:

- ! **Urinary retention.** Your bladder does not empty or does not empty completely when you urinate.
- ! **Gastric retention.** Your stomach empties slowly or incompletely after a meal.
- ! **Uncontrolled narrow-angle glaucoma (high blood pressure in your eye).** Tell your doctor if you have glaucoma or a family history of glaucoma.
- ! **Pregnancy or breastfeeding.** Tell your doctor if you are pregnant, or become pregnant, or are breastfeeding. OXYTROL may not be right for you.
- ! **Allergy to oxybutynin or the inactive ingredients in OXYTROL.** See **What are the ingredients of Oxytrol.** If you have had allergies to medical tape products or other skin patches, tell your doctor.

If you have certain other medical conditions, use OXYTROL with caution. Tell your doctor about all your medical conditions, especially if you have any of the following:

- ! Liver disease
- ! Kidney disease

- ! Bladder obstruction (blockage)
- ! Gastrointestinal obstruction (blockage in the digestive system)
- ! Ulcerative colitis (inflamed bowels)
- ! Myasthenia gravis (nerve weakness)
- ! Reduced gastrointestinal motility (chronic constipation)
- ! Gastric reflux disease (heartburn) or esophagitis (inflamed esophagus, the tube between your mouth and stomach), and / or if you are taking drugs that may worsen esophagitis such as biphosphonates (a type of bone loss preventing drug)

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and supplements. Some of them may cause problems if you take OXYTROL. Also OXYTROL may affect how some of them work.

**What should I avoid while using OXYTROL?**

Do not expose the patch to sunlight. Therefore wear it under clothing.

**What are the possible side effects of OXYTROL?**

You may see mild redness at the site when a patch is removed. This redness should disappear within several hours after removing the patch. If uncomfortable irritation or excessive itchiness continues, tell your doctor.

Oxybutynin may cause sleepiness or blurred vision, so be careful when driving or operating machinery. In addition, sleepiness may be increased by drinking alcohol (beer,

wine or hard liquor). Oxybutynin therapy has also been associated with skin rash, painful urination, nausea, abdominal pain, back pain, and fatigue.

Since oxybutynin treatment may decrease sweating, you may overheat or have fever or heat stroke if you are in warm or hot temperatures.

The most common side effects of OXYTROL are skin reactions where the patch is put on. These include itching and redness. Other side effects include dry mouth, constipation, abnormal vision and headache. If you take other medicines that cause dry mouth, constipation, or sleepiness, OXYTROL can increase those effects.

These are not all the side effects of OXYTROL. For a complete list, ask your doctor or pharmacist.

### **How should I use OXYTROL?**

Put on a new patch of OXYTROL 2 times a week (every 3 to 4 days) according to your doctor's instructions. Wear the patch all the time until it is time to apply a new one.

Wear only 1 patch of OXYTROL at a time. Try to change the patch on the same 2 days each week. Your package of OXYTROL has a calendar checklist printed on the back to help you remember your schedule. Mark the schedule you plan to follow. Always change OXYTROL on the 2 days of the week you mark on the calendar.

abdomen      hips      buttocks

Put the patch on a clean, dry and smooth (fold-free) area of skin on your abdomen (stomach area), hips or buttocks (as shown in the picture). Avoid your waistline area, since tight clothing may rub against the patch. The areas you choose should not be oily, damaged (cut or scraped), irritated (rashes) or have any other skin problems. Do not put OXYTROL on areas that have been treated with oils, lotions, or powders that could keep the patch from sticking well to your skin.

When you put on a new patch, use a different area of skin from the most recent patch site. You may find it useful to change the site from one side of your body to the other. Do not use the same area for the patch for at least 1 week. You may wish to try different locations when using OXYTROL to find the locations that are most comfortable for you and where clothing will not rub against it.

Each patch is sealed in its own protective pouch. When you are ready to put on the OXYTROL patch, tear open the pouch and remove the patch. Apply the patch to your skin right away. Do not keep or store the patch outside the sealed pouch.

The sticky adhesive side of the patch is covered by 2 strips of overlapping protective liner. Remove the first piece of the protective liner and place the patch, adhesive face down, firmly on to the skin.

Bend the patch in half and gently roll the remaining part onto your skin using the tips of your fingers. As you roll the patch in place, the second piece of the protective liner should move off the patch. Apply firm pressure over the surface of the patch with your fingers to make sure the patch stays on. When putting on the patch, avoid touching the sticky adhesive side. Touching the adhesive may cause the patch to fall off early. Throw away the protective liners.

Contact with water when you are bathing, swimming, showering or exercising will not change the way that OXYTROL works. However, try to avoid rubbing the patch area during these activities.

If the patch partly or completely falls off, press it back in place and continue to follow your application schedule. If the patch does not stay on, throw it away. You should then put on a new patch in a different area, but continue to follow your original application schedule. If you forget to change your patch after 3 or 4 days, remove the old patch, put on a new patch in a different area and continue to follow your original application schedule.

When changing Oxytrol, remove the old patch slowly and carefully avoid damaging the skin. Once off, fold the patch in half with the sticky sides together and insert the used patch into the newly opened pouch of the replacement system. Since the patch will still contain some oxybutynin, throw it away so that it cannot be accidentally worn or swallowed by another person, especially a child, or a pet.

Gently washing the application site with warm water and a mild soap should remove any adhesive that stays on your skin after removing the patch. A small amount of baby oil may also be used to remove any excess residue. Rings of adhesive that become dirty may require a medical adhesive removal pad that you can get from your pharmacist. Alcohol or other dissolving liquids (nail polish remover or other solvents) may cause skin irritation and should not be used.

Store at room temperature at 15 - 30 EC. Protect from moisture and humidity. Keep OXYTROL and all medications in a safe, secure place and out of the reach of children.

**General advice about OXYTROL**

Do not give OXYTROL to other people, even if they have the same symptoms you have.

It may harm them.

This leaflet summarizes the most important information about OXYTROL. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about OXYTROL that is written for health professionals. You can get more information about OXYTROL from the product information department at 1-888-OXYTROL (1-888-699-8765) or by selecting patient information at the OXYTROL website located at [www.OXYTROL.com](http://www.OXYTROL.com).

Manufactured by: Watson Laboratories, Inc., 417 Wakara Way, UT, 84108, USA  
Distributed by: Paladin Labs Inc., Montréal, Canada, H4P 2T4

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## PHARMACOLOGY

### Pharmacodynamics

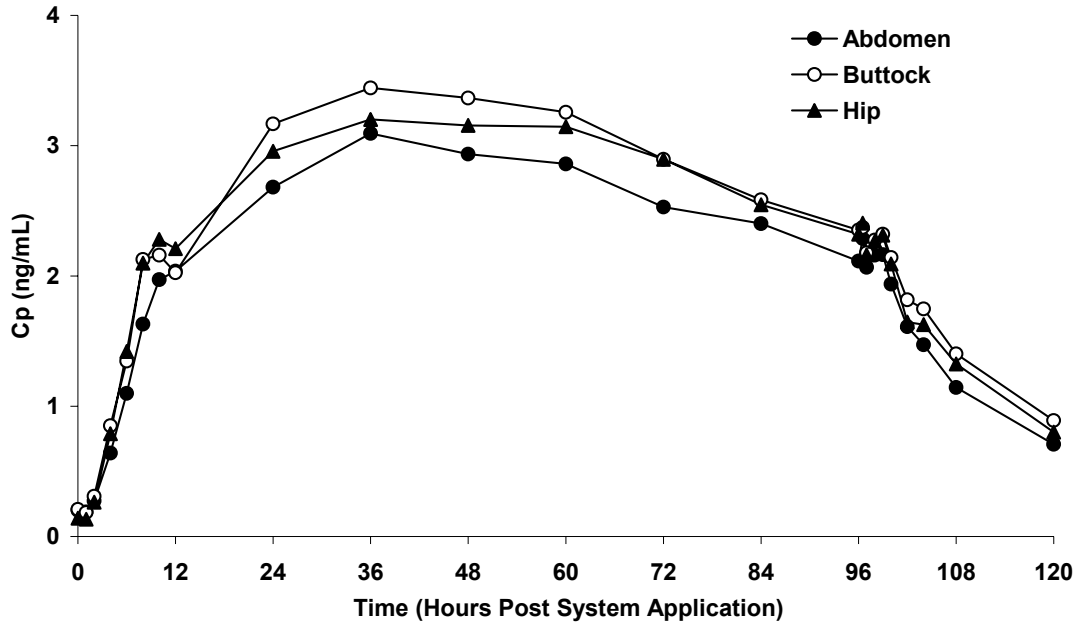
Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with overactive bladder, characterized by detrusor muscle instability or hyperreflexia, cystometric studies have demonstrated that oxybutynin 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.

### Pharmacokinetics

#### Absorption

Oxybutynin is transported across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. The average daily dose of oxybutynin absorbed from the 39 cm<sup>2</sup> **OXYTROL™** systems is 3.9 mg. The average (SD) nominal dose, 0.10 (0.02) mg oxybutynin per cm<sup>2</sup> surface area, was obtained from analysis of residual oxybutynin content of systems worn over a continuous 4-day interval during 303 separate occasions in 76 healthy volunteers. Following application of the first **OXYTROL™** 3.9 mg/day system, oxybutynin plasma concentrations increase 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 randomized, crossover study of the three recommended application sites in 24 healthy men and women are shown in Figure 1.



**Figure 1: Average plasma oxybutynin concentrations (Cp) in 24 healthy male and female volunteers during single-dose application of OXYTROL™ 3.9 mg/day to the abdomen, buttock and hip (System 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 2).

**Figure 2: Average (SEM) steady-state oxybutynin and N-desethyloxybutynin plasma concentrations (C<sub>p</sub>) measured in 13 healthy volunteers following the second transdermal system application in a multiple-dose, randomized, crossover study.**

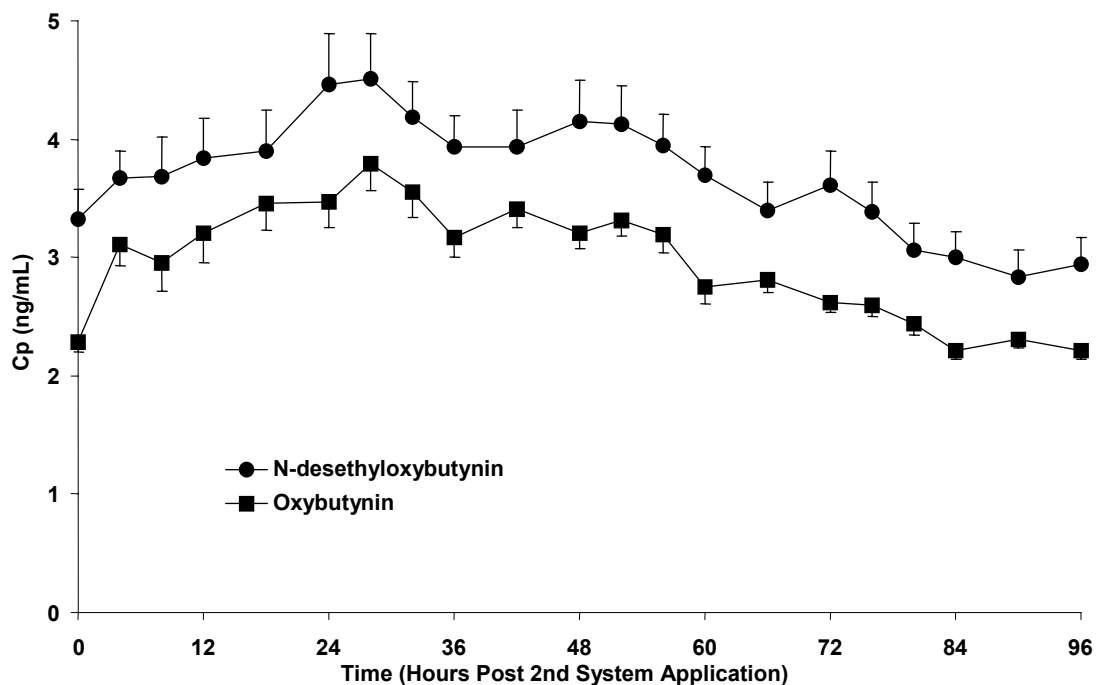


Table 3 provides a summary of pharmacokinetic parameters of oxybutynin in healthy volunteers after single and multiple applications of **OXYTROL™**.

**Table 3: Mean (SD) oxybutynin pharmacokinetic parameters from a single and multiple dose studies in healthy men and women volunteers after application of OXYTROL™ on the abdomen.**

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

1 T<sub>max</sub> given as median

2 AUC<sub>inf</sub>

3 AUC<sub>0-96</sub>

4 AUC<sub>0-84</sub>

### 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.

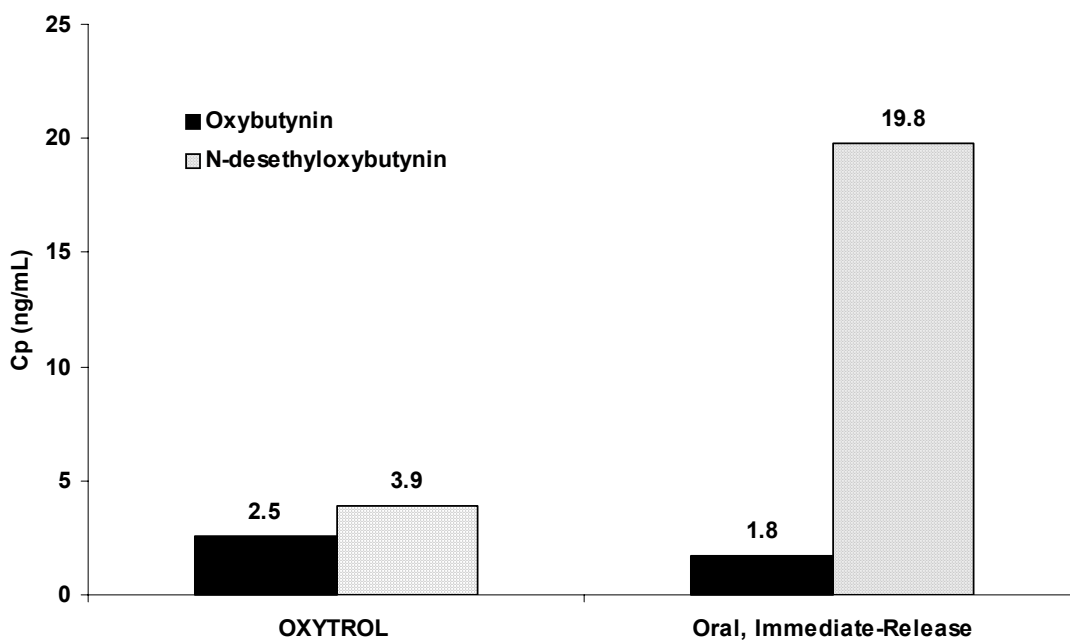
### Metabolism

Oxybutynin is metabolized 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 3). 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 3). 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 3: Average plasma concentrations (C<sub>p</sub>) measured after a single, 96-hour application of the OXYTROL™ 3.9 mg/day system (AUC<sub>inf</sub>/96) and a single, 5 mg, oral immediate-release dose of oxybutynin chloride (AUC<sub>inf</sub>/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 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 N-desethyloxybutynin.

### **Special Populations**

#### Gender:

Analysis of pharmacokinetic data from Phase I studies indicates that females exhibit a slightly greater metabolism of oxybutynin than males. This is consistent with the known higher cytochrome CYP 3A4 activity in females (Beirle et al 1999). However, gender differences were not detected in the analysis of steady-state levels of oxybutynin and N-desethyloxybutynin in patients with over-active bladder during clinical development.

#### Geriatric:

Age was not found to have a significant effect on steady-state levels of oxybutynin and N-desethyloxybutynin in patients with over-active bladder, including patients up to the age of 88 years.

#### Race:

Race was not found to have a significant effect on steady-state levels of oxybutynin and N-desethyloxybutynin.

#### Pediatric:

Pharmacokinetic and clinical studies were not conducted in pediatric patients for the indication of over-active bladder.

### Hepatic and Renal Insufficiency:

Pharmacokinetic trials were not conducted in this patient population during the development program for Oxytrol™

### **Clinical Studies**

The efficacy and safety of **OXYTROL™** were evaluated in patients with urge, urinary incontinence in two Phase III controlled studies and one open-label extension. Study 1 was a Phase III, placebo-controlled study, comparing the safety and efficacy of **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 III study, comparing the safety and efficacy of **OXYTROL™** 3.9 mg/day versus active and placebo controls in 361 patients.

#### Study 1

Study 1 was a randomized, 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 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  $\geq 10$  per week and  $\geq 8$  micturitions per day. The patient's medical history and urinary diary during a 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 summarized in Table 4.

**Table 4: 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		OXYTROL™ 3.9 mg/mL	
	N		N	
	127		120	
	Mean (SD)	Median	Mean (SD)	Median
<b>Weekly incontinence episodes</b>				
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*	
<b>Daily urinary frequency</b>				
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*	
<b>Urinary void volume (mL)</b>				

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

Study 2 was a randomized, double-blind, double-dummy, study of **OXYTROL™** 3.9 mg/day versus an active comparator (tolterodine oral treatment 4 mg daily long-acting capsules) versus placebo, conducted in 361 patients. 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 summarized in Table 5.

**Table 5: 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 2)**

<b>Parameter</b>	<b>Placebo</b>		<b>OXYTROL™ 3.9 mg/mL</b>	
<b>N</b>	<b>117</b>		<b>121</b>	
	<b>Mean (SD)</b>	<b>Median</b>	<b>Mean (SD)</b>	<b>Median</b>
<b>Daily incontinence episodes</b>				
Baseline	5.0 (3.2)	4	4.7 (2.9)	4
Reduction	2.1 (3.0)	2	2.9 (3.0)	3
p value vs. Placebo	-		0.0137*	
<b>Daily urinary frequency</b>				
Baseline	12.3 (3.3)	12	12.4 (2.9)	12
Reduction	1.4 (2.7)	1	1.9 (2.7)	2
p value vs. Placebo	-		0.1010*	
<b>Urinary void volume (mL)</b>				
Baseline	175.0 (68.0)	171.0	164.8 (62.3)	160
Increase	9.3 (63.1)	5.5	32.0 (55.2)	24
p value vs. Placebo	-		0.0010*	

\* Comparison significant if  $p < 0.05$

**Adhesion**

The adhesion of Oxytrol™ to the skin of patients was assessed during the conduct of the two phase III trials described above (see **Clinical Studies**). In Study 2, 361 active and placebo patients had 993 transdermal systems evaluated for adhesion. The patches were found to be at least 75% adhered in 99% of the cases, with detachment being noted at the edges only, and complete adherence being documented in 92% of the patients. There were no reports of the patch becoming completely detached in this study.

In assessing the adhesion characteristics of the Oxytrol™ Transdermal System during Study 1, 300 systems were evaluated in 97 patients. The adhesion assessment results were similar, but two Oxytrol™ systems did become completely detached.

**TOXICOLOGY****Acute Toxicity**

The estimated minimal lethal dose of single subcutaneous administration of oxybutynin to rats was > 12,000 mg/kg. Survivors had decreased motor activity and unsteady gaits. Anticholinergic and smooth muscle relaxation effects, such as mydriasis, were seen at all doses tested. At the site of injection, induration was observed at 3000 mg/kg dose and above.

In dogs subcutaneous administration of oxybutynin at 2000 mg/kg, the highest dose tested, was not lethal. All other doses tested, including the lowest dose of 125 mg/kg, caused signs of pronounced anticholinergic activity. There was decrease or disappearance of pupil light reflex, nasal dryness, salivary decrease and constipation. Reactions at the administration site included tylosis, induration or ulcer and were likely due to irritant effects. The two high doses used (500 and 2000 mg/kg) generated peak plasma concentrations of oxybutynin in the range of 399 - 719 ng/mL and AUC values above 20,000 ng.hr/mL.

Oxybutynin administration by the percutaneous route at approximately 1300 mg/m<sup>2</sup>, representing exposure to about 10% of body surface, did not cause lethality. Transient pharmacological effects, such as mydriasis and decrease of pupil light reflex were observed at all doses tested. No other specific effects were observed. The systemic exposure of 1300 mg/m<sup>2</sup> percutaneous dose was about 10% of that for 125 mg/kg given subcutaneously.

### **Repeat-Dose Toxicity**

Repeated doses of oxybutynin were subcutaneously administered for thirteen weeks to rats (0, 1.2, 9 or 72 mg/kg/every 3rd day). The dose was administered every third day for 90 days. The following reactions were observed: mydriasis at all dose levels; increased water intake and urine volume at 9 and 72 mg/kg. The only other effect at 1.2 mg/kg was an increase in blood cell count which was exacerbated at the highest dose level. Other observations included induration, ulcer, encrustation at administration sites and increased

leucocytes. Non-specific effects such as inhibition of weight gain and decreased food intake suggested deterioration in general health. No other specific effects or gender differences were noted. No significant histopathology was recorded.

Toxicokinetic data indicate little accumulation of exposure for the two lower dose levels but greater plasma exposure to oxybutynin on Day 84 than on day 1 for the 72 mg/kg regimen.

For dogs, the dose levels administered every third day were 1.2, 6 and 30 mg/kg and there were 3 animals/sex/group. Mydriasis occurred at the lowest dose, as did some local administration site effects and changes in blood biochemistry. Higher doses produced anticipated toxicity.

### **Carcinogenicity Studies**

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity.

### **Genotoxicity and Reproductive Studies**

The mutagenic potential of oxybutynin was tested by a bacterial reversion assay in *Escherichia coli* and *Salmonella typhimurium* test systems and was found to be negative.

A chromosomal aberration test in mammalian cells *in vitro* and micronucleus assay in the bone marrow of mice were also negative. In summary, no evidence for genotoxic potential was observed.

In reproductive studies in rats, the no effect dose for female fertility was close to 5 mg/kg/day. 125 mg/kg/day did not affect primary blastogenesis. The rate of implantation and mortality in rats were not statistically significantly changed at 125 mg/kg, but live embryo count was reduced at 25 and 125 mg/kg, indicating a need for caution when considering the use of oxybutynin in pregnant humans.

In rabbits, maternal toxicity was observed at quite low doses (less than 1 mg/kg). Nevertheless, the incidence of abnormalities in surviving neonates did not increase with doses up to 25 mg/kg oxybutynin.

Reproductive toxicology studies in rat and rabbit indicated a slight increase in foetal malformations in rats, together with lengthened gestation and impaired post-natal thriving, at doses associated with maternal toxicity. Lower doses (20 mg/kg) were without adverse effect in rats and there were no effects in rabbits at 48 mg/kg on embryo-foetal development, despite maternal toxicity.

In summary, reproduction studies with oxybutynin chloride in the rat and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus .

### **Local Tolerance Studies**

No dermal phototoxicity was observed following oxybutynin application with ultraviolet irradiation to guinea pigs for 24 hours. Oxybutynin patches did not produce delayed contact sensitization.

The primary dermal irritation index was calculated to be 0.8 (barely perceptible irritant) for the placebo patch and 1.9 (slight irritant) for the oxybutynin patch.

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