

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXYTROL safely and effectively. See full prescribing information for OXYTROL.

OXYTROL® (oxybutynin transdermal system)

Initial U.S. Approval: 1975

RECENT MAJOR CHANGES

Warnings and Precautions, Central Nervous System Effects (5.3) 07/2015

INDICATIONS AND USAGE

OXYTROL is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. (1)

DOSAGE AND ADMINISTRATION

- Apply OXYTROL transdermal system twice weekly (every 3 to 4 days) to dry, intact skin on the abdomen, hip, or buttocks. (2)
- Select a new application site with each new system to avoid re-application to the same site within 7 days. (2)

DOSAGE FORMS AND STRENGTHS

Transdermal system: 3.9 mg/day (3)

CONTRAINDICATIONS

- Urinary retention (4)
- Gastric retention (4)
- Uncontrolled narrow-angle glaucoma (4)
- Known serious hypersensitivity reaction to OXYTROL, oxybutynin, or to any of the components of OXYTROL (4)

WARNINGS AND PRECAUTIONS

- Urinary Retention: Use caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention. (5.1)

- Gastrointestinal Disorders: Use caution in patients with gastrointestinal obstructive disorders or decreased intestinal motility because of the risk of gastric retention. Use caution in patients with gastroesophageal reflux and/or those taking drugs that can cause or exacerbate esophagitis. (5.2)
- Central Nervous System Effects: Somnolence has been reported with products containing oxybutynin. Advise patients not to drive or operate heavy machinery until they know how OXYTROL affects them. (5.3)
- Angioedema: Angioedema has been reported with oral oxybutynin use. If symptoms of angioedema occur, discontinue OXYTROL and initiate appropriate therapy. (5.4)
- Skin Hypersensitivity: Discontinue OXYTROL in patients with skin hypersensitivity. (5.5)
- Myasthenia gravis: Use with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction. (5.6)

ADVERSE REACTIONS

The most common adverse reactions (incidence > 5% and > placebo) are application site reactions and dry mouth. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Watson Pharmaceuticals, Inc. at 1-800-272-5525 or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Other Anticholinergics (muscarinic antagonists): Concomitant use with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, and other anticholinergic pharmacological effects. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2015

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OXYTROL is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

2 DOSAGE AND ADMINISTRATION

OXYTROL 3.9 mg/day should be applied to dry, intact skin on the abdomen, hip, or buttock twice weekly (every 3 or 4 days). A new application site should be selected with each new system to avoid re-application to the same site within 7 days.

3 DOSAGE FORMS AND STRENGTHS

Transdermal System: 3.9 mg/day

4 CONTRAINDICATIONS

The use of OXYTROL is contraindicated in the following conditions:

- Urinary retention
- Gastric retention
- Uncontrolled narrow-angle glaucoma
- Known serious hypersensitivity reaction to OXYTROL, oxybutynin, or to any of the components of OXYTROL [*see Warnings and Precautions (5.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Urinary Retention

Administer OXYTROL with caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

5.2 Risks in Patients with Gastrointestinal Disorders

Administer OXYTROL with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention.

OXYTROL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis or intestinal atony.

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.

5.3 Central Nervous System Effects

Products containing oxybutynin are associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including headache, dizziness, somnolence, confusion and hallucinations. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment. Advise patients not to drive or operate heavy machinery until they know how OXYTROL affects them. If a patient experiences anticholinergic CNS effects, drug discontinuation should be considered.

5.4 Angioedema

Angioedema requiring hospitalization and emergency medical treatment has occurred with the first or subsequent doses of oral oxybutynin. In the event of angioedema, OXYTROL should be discontinued and appropriate therapy promptly provided.

5.5 Skin Hypersensitivity

Patients who develop skin hypersensitivity to OXYTROL should discontinue drug treatment.

5.6 Exacerbation of Symptoms of Myasthenia Gravis

Administer OXYTROL with caution to patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of OXYTROL was evaluated in a total of 417 patients who participated in two clinical efficacy and safety studies and an open-label extension. Additional safety information was collected in earlier phase trials. In the two pivotal studies, 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 reactions reported in the pivotal trials are summarized in Tables 1 and 2 below.

Table 1: Number (%) of adverse reactions occurring in $\geq 2\%$ of OXYTROL-treated patients and greater in the OXYTROL group than in the placebo group (Study 1).

Adverse Reaction	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%

Table 2: Number (%) of adverse reactions occurring in $\geq 2\%$ of OXYTROL-treated patients and greater in the OXYTROL group than in the placebo group (Study 2).

Adverse Reaction	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%

Most adverse reactions 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.

Adverse reactions 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

discontinuations were due 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 reactions were: application site pruritus, application site erythema, and dry mouth.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of OXYTROL. Because these reactions 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.

Nervous System Disorders: dizziness, somnolence, confusion

Psychiatric Disorders: hallucinations

7 DRUG INTERACTIONS

No specific drug-drug interaction studies have been performed with OXYTROL.

7.1 Other Anticholinergics

The concomitant use of OXYTROL 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.

7.2 Cytochrome P450 Inhibitors

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).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies using OXYTROL in pregnant women. OXYTROL should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during OXYTROL treatment are encouraged to contact their physician.

Risk summary

Based on animal data, oxybutynin is predicted to have a low probability of increasing the risk of adverse developmental effects above background risk.

Animal Data

In a rat embryo/fetal developmental toxicity study, pregnant rats received up to 25 mg/kg subcutaneously of oxybutynin chloride. Maternal systemic exposure was estimated to be 50 times that of women treated at the maximum recommended human dose (MRHD) of 36 mg, based on body surface area. No embryo/fetal toxicity was observed in rats under the conditions of this study.

In a rabbit embryo/fetal developmental toxicity study, pregnant rabbits received oxybutynin chloride at up to 0.4 mg/kg subcutaneously. Maternal systemic exposure was estimated to be about equal that of women treated at the MRHD of 36 mg, based on body surface area. No embryo/fetal toxicity was observed in rabbits under the conditions of this study.

In mouse and hamster embryo/fetal development studies, no embryo/fetal toxicity was observed.

8.3 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.

8.4 Pediatric Use

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

8.5 Geriatric Use

Forty-nine percent of OXYTROL-treated patients in the clinical studies were at least 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, 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 [*see Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

The safety and efficacy of OXYTROL have not been established in patients with renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of OXYTROL have not been established in patients with hepatic impairment.

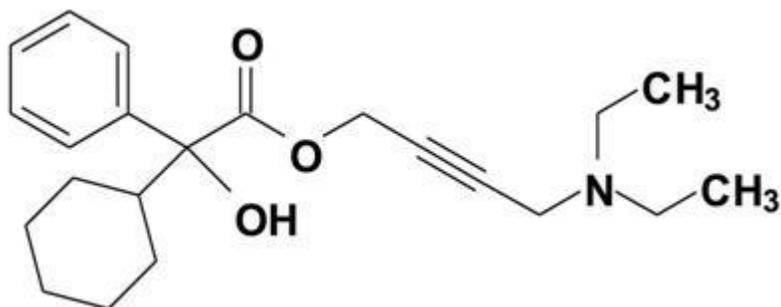
10 OVERDOSAGE

The plasma concentration of oxybutynin declines within 1 to 2 hours after removal of transdermal system(s). Patients should be monitored until symptoms resolve. 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 chloride 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 treatment directed at their symptoms.

11 DESCRIPTION

OXYTROL (oxybutynin transdermal system) is designed to deliver oxybutynin over a 3- to 4-day interval after application to intact skin. OXYTROL is available as a 39 cm² system containing 36 mg of oxybutynin. OXYTROL has a nominal *in vivo* delivery rate of 3.9 mg oxybutynin per day through skin of average permeability (inter-individual variation in skin permeability is approximately 20%).

Oxybutynin is an antispasmodic, anticholinergic agent. Oxybutynin is administered as a racemate of R- and S-isomers. Chemically, oxybutynin is d, l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate. The empirical formula of oxybutynin is C₂₂H₃₁NO₃. Its structural formula is:

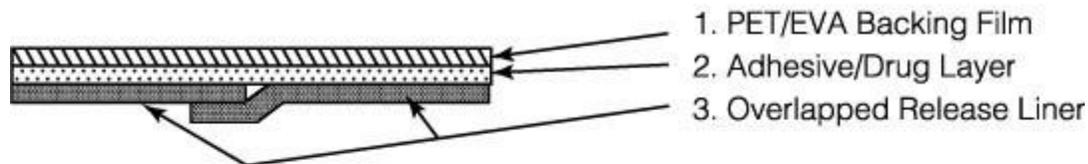


Oxybutynin is a white powder with a molecular weight of 357. It is soluble in alcohol, but relatively insoluble in water.

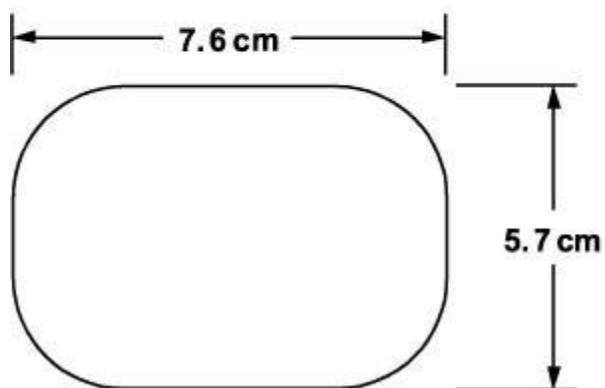
OXYTROL is a matrix-type transdermal system composed of three layers as illustrated in Figure 1. Layer 1 (Backing Film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 (Adhesive/Drug 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.

Figure 1: Side and top views of the OXYTROL system.
(Not to scale)

Side View



Top View



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 characterized by involuntary detrusor contractions, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction.

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.

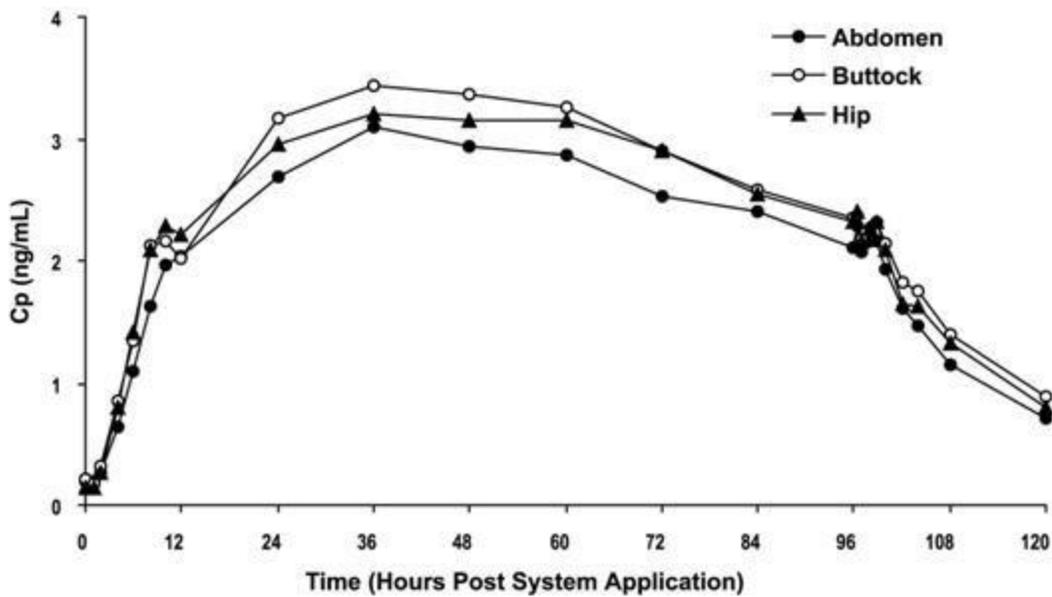
12.3 Pharmacokinetics

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 cm² OXYTROL system 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 systems 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 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 2.

Figure 2: 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 3). Table 3 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 transdermal system application in a multiple-dose, randomized, crossover study.

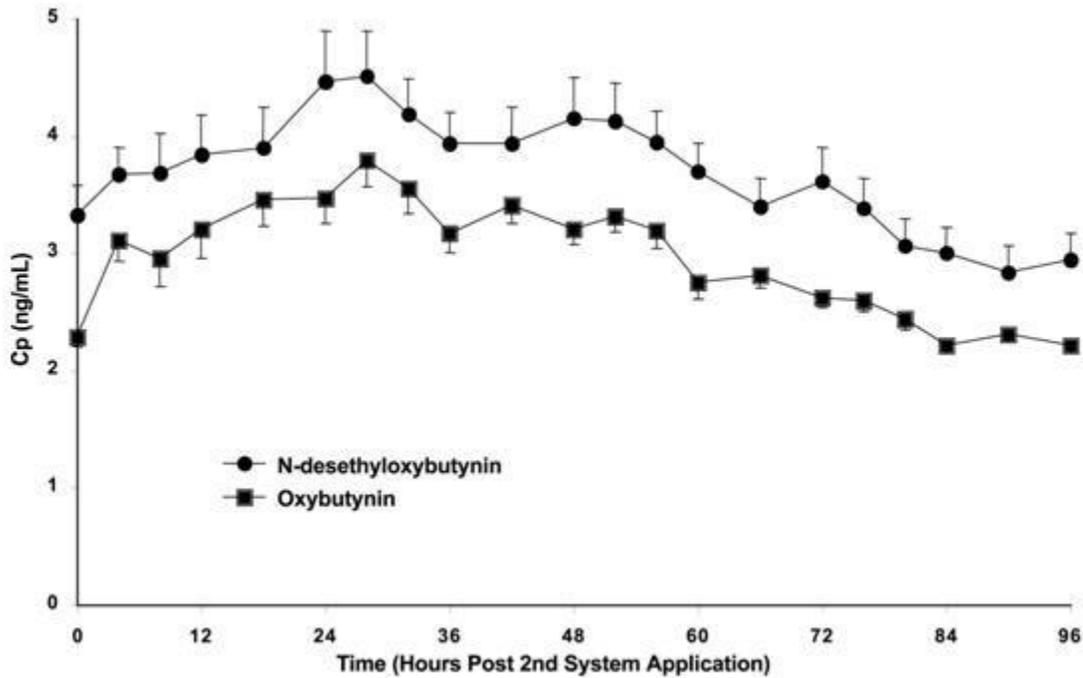


Table 3: Mean (SD) oxybutynin pharmacokinetic parameters from single and multiple dose studies in healthy men and women volunteers after application of OXYTROL on the abdomen.

Dosing	Oxybutynin			
	C_{max} (SD) (ng/mL)	T_{max} ¹ (hr)	C_{avg} (SD) (ng/mL)	AUC (SD) (ng/mLxh)
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 median

² AUC_{inf}

³ AUC_{0-96}

⁴ AUC_{0-84}

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.

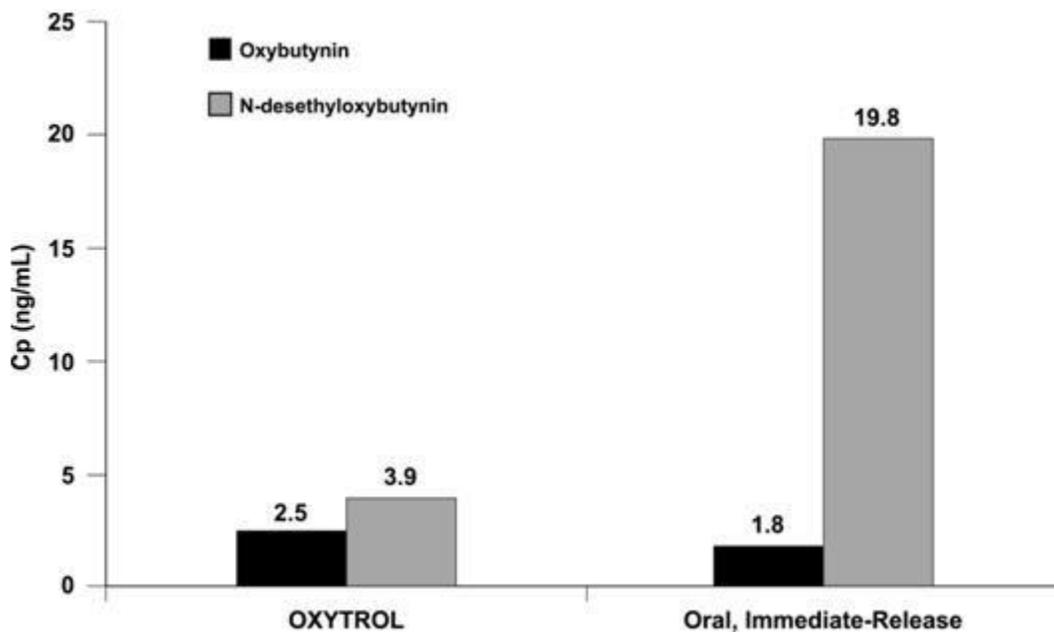
Metabolism

Oxybutynin is 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 4). The plasma concentration area under the time-concentration curve (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 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 OXYTROL 3.9 mg/day system (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 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.

Specific Populations:

Renal Impairment: The effects of renal impairment on the pharmacokinetics of oxybutynin and N-desethyloxybutynin are not known.

Hepatic Impairment: The effects of hepatic impairment on the pharmacokinetics of oxybutynin and N-desethyloxybutynin are not known.

Geriatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were similar in older and younger patients .

Pediatric: The pharmacokinetics of oxybutynin and N-desethyloxybutynin were not evaluated in individuals younger than 18 years of age.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum exposure in humans taking an oral dose based on body surface area.

Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis*, *Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems. Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

14 CLINICAL STUDIES

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

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 an OXYTROL dose of 3.9 mg/day or 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. Changes 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 (N = 127)		OXYTROL 3.9 mg/day (N = 120)	
	Mean (SD)	Median	Mean (SD)	Median
<i>Weekly Incontinence Episodes</i>				
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*	
<i>Daily Urinary Frequency</i>				
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*	
<i>Urinary Void Volume (mL)</i>				
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**
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*Comparison significant if $p < 0.05$

**Comparison significant if $p \leq 0.0167$

Study 2 was a randomized, double-blind, 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 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. Changes 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).

Parameter	Placebo (N = 117)		OXYTROL 3.9 mg/day (N = 121)	
	Mean (SD)	Median	Mean (SD)	Median
<i>Daily Incontinence Episodes</i>				
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*	
<i>Daily Urinary Frequency</i>				
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*	
<i>Urinary Void Volume (mL)</i>				
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*
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*Comparison significant if $p < 0.05$

In a controlled clinical trial of skin sensitization, none of the 103 test subjects demonstrated skin hypersensitivity to OXYTROL.

Adhesion

Adhesion was periodically evaluated during the pivotal studies. Of the 4,746 OXYTROL evaluations in the 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 systems evaluated in the pivotal studies were assessed as being $\geq 75\%$ attached and thus would be expected to perform as anticipated.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Unit Dose: Heat sealed pouch containing 1 OXYTROL (oxybutynin transdermal system).

Each 39 cm² system imprinted with “OXYTROL 3.9 mg/day” contains 36 mg of oxybutynin for nominal delivery of 3.9 mg oxybutynin per day when dosed in a twice weekly regimen.

NDC 52544-920-08 Patient Calendar Box of 8 Systems

Storage

Store at 20-25°C (68-77°F). [See USP controlled room temperature.] Protect from moisture and humidity. Do not store outside the sealed pouch. Apply immediately after removal from the protective pouch. Discard used OXYTROL in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (*Patient Information and Instructions for Use*)

Instructions for Use

Inform patients that OXYTROL should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new system to avoid re-application to the same site within 7 days. Inform patients that details on use of the system are explained in the Patient Information Leaflet.

Inform patients to discard used OXYTROL in household trash in a manner that prevents accidental application or ingestion by children, pets, or others. Inform patients to keep out of reach of children.

Important Anticholinergic Adverse Reactions

Patients should be informed that anticholinergic (antimuscarinic) agents, such as OXYTROL, may produce adverse reactions related to anticholinergic pharmacological activity including:

- Urinary retention and constipation.
- Heat prostration (due to decreased sweating) when anticholinergics such as OXYTROL are used in a hot environment.
- Dizziness or blurred vision. Patients should be advised to avoid driving or operating heavy machinery until OXYTROL's effects have been determined.
- Drowsiness that may be worsened by alcohol.
- Angioedema has been reported with oral oxybutynin use. Patients should be advised to promptly discontinue OXYTROL and seek immediate medical attention if they experience symptoms consistent with angioedema.

For all medical inquiries contact:

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PATIENT INFORMATION
OXYTROL (oxe-tröl)
(oxybutynin transdermal system)

Read this Patient Information before you start taking OXYTROL and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is OXYTROL?

OXYTROL is a transdermal system (skin patch) for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. It delivers the active ingredient, oxybutynin, directly into your bloodstream through your skin.

Overactive bladder makes it hard to urinate (passing 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).

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

It is not known if OXYTROL is safe and effective in children.

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 pressure in your eye).** Tell your doctor if you have glaucoma or a family history of glaucoma.
- **Allergy to oxybutynin or the inactive ingredients in OXYTROL.** If you are allergic to oxybutynin or any of the ingredients in OXYTROL. See the end of this leaflet for a complete list of ingredients in OXYTROL. If you have allergies to medical tape products or other skin patches, tell your doctor.

What should I tell my doctor before using OXYTROL?

Before you take OXYTROL, tell your doctor if you:

- have liver problems
- have kidney problems
- have problems emptying your bladder completely
- have a gastrointestinal obstruction (blockage in the digestive system)
- have ulcerative colitis (inflamed bowels)
- have gastric reflux disease or esophagitis (inflamed esophagus, the tube between your mouth and stomach)
- have Myasthenia Gravis (generalized muscle weakness)
- are pregnant or plan to become pregnant. It is not known if OXYTROL will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if OXYTROL passes into your breast milk. You and your doctor should decide if you will take OXYTROL or breastfeed.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and herbal supplements.

Using OXYTROL with certain other medicines may affect each other. Using OXYTROL with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- medicines called “bisphosphonates” to treat osteoporosis
- medicines called “anticholinergics”

Ask your doctor or pharmacist for a list of these medicines if you are not sure if this is your medicine.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I use OXYTROL?

- Read the Instructions for Use at the end of this Patient Information Leaflet for information on the right way to use OXYTROL.
- Use OXYTROL exactly as your doctor tells you to use it.
- Put on a new patch of OXYTROL 2 times a week (every 3 to 4 days) according to your doctor’s instructions.
- Choose a new skin site for each new patch application. You should not use the same skin site within 7 days.
- 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.
- Contact with water when you are bathing, swimming, showering or exercising will not change the way that OXYTROL works.

What should I avoid while using OXYTROL?

- You should not drink alcohol while using OXYTROL. It can increase your chance of getting serious side effects.
- OXYTROL can cause dizziness or blurred vision. **Do not** drive or operate machinery, or do other dangerous activities until you know how OXYTROL affects you.
- **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. **Do not** expose the patch to sunlight. Wear your patch under clothing.
- Avoid rubbing the patch area during bathing, swimming, showering or exercising.

What are the possible side effects of OXYTROL?

OXYTROL may cause serious side effects, including:

- **inability to empty your bladder (urinary retention).** OXYTROL may increase your chances of not being able to empty your bladder if you have bladder outlet obstruction. Tell your doctor right away if you are unable to empty your bladder.
- **increased risk of stomach problems in certain patients.** OXYTROL may cause stomach problems in patients who have a history of ulcerative colitis, intestinal atony, gastrointestinal reflux, or who are taking certain medicines called bisphosphonates.

- **central nervous system effects.** OXYTROL can cause central nervous system effects including headache, dizziness, and sleepiness. Your doctor should monitor you for these effects after starting OXYTROL. See “What should I avoid while using OXYTROL.”
- **swelling (angioedema).** The active ingredient in OXYTROL, oxybutynin, can cause swelling around the eyes, lips, genitals, hands or feet. Some people who have taken oxybutynin medicines by mouth have had to be hospitalized. Stop using OXYTROL immediately and seek emergency treatment right away if you have any of these symptoms.
- **skin hypersensitivity.** You may have skin changes where the patch was placed such as itching, rash, or redness. Tell your doctor if these changes do not go away or bother you.
- **worsening of myasthenia gravis.** OXYTROL can make symptoms worse in people who have myasthenia gravis. See “What should I tell my doctor before using OXYTROL?”

The most common side effects of OXYTROL include skin reactions where the patch is placed and dry mouth.

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

Tell your doctor if you have any side effect that bothers you or that does not go away or if you have constipation.

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

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store OXYTROL?

- Store OXYTROL at 68°F to 77°F (20°C to 25°C).
- Do not store OXYTROL outside the sealed pouch.
- Keep OXYTROL patches in a dry place.

Keep OXYTROL and all medicines out of the reach of children.

General information about the safe and effective use of OXYTROL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use OXYTROL for a condition for which it was not prescribed. Do not give OXYTROL to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about OXYTROL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about OXYTROL that is written for health professionals.

For more information, go to www.OXYTROL.com website or call 1-888-699-8765 (1-888-OXY-TROL).

What are the ingredients of OXYTROL?

Active Ingredient: oxybutynin

Inactive Ingredients: Flexible polyester/ethylene-vinyl acetate film, acrylic adhesive, triacetin, siliconized polyester film.

Instructions for Use
OXYTROL (oxe-tröl)
(oxybutynin transdermal system)

Read this Instructions for Use that comes with your OXYTROL before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

Where to apply OXYTROL:

- Put the patch on a clean, dry, and smooth (fold-free) area of skin on your abdomen (stomach area), hips or buttocks. **See Figure A.**
- 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 choose to try different sites when using OXYTROL to find the sites that are most comfortable for you and where clothing will not rub against it.

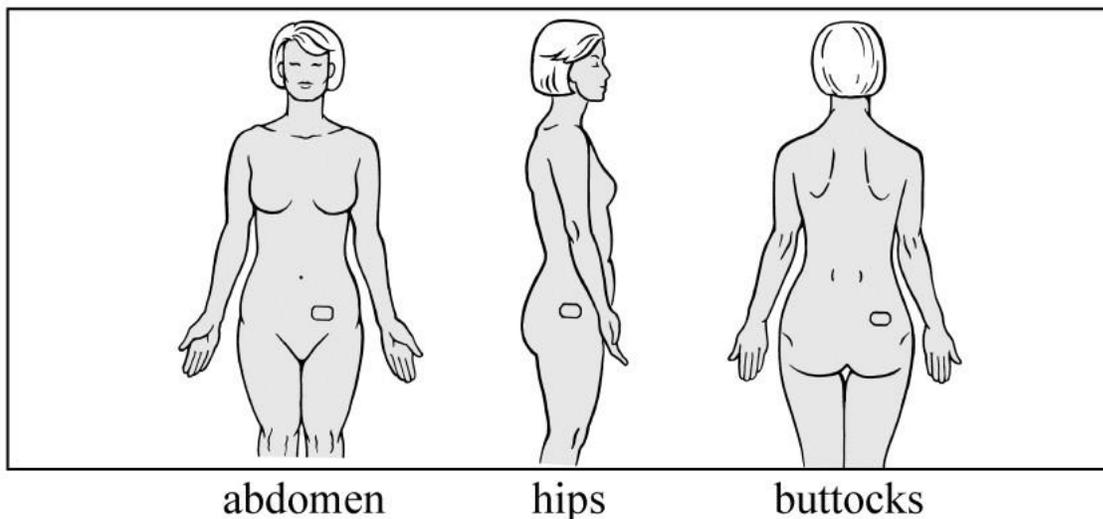


Figure A

How to apply OXYTROL:

Step 1.

- Each patch is sealed in its own protective pouch. **See Figure B.**
- When you are ready to put on your OXYTROL patch, tear open the pouch and remove the patch. **See Figure C.**

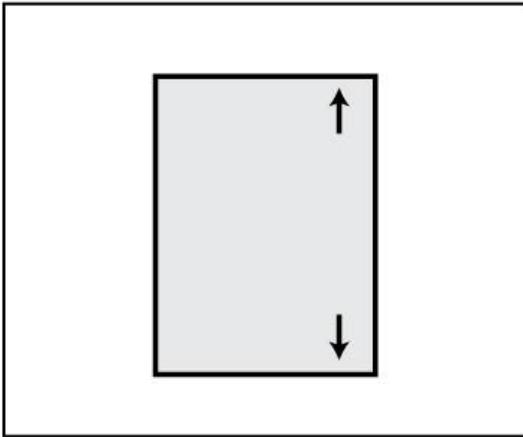


Figure B

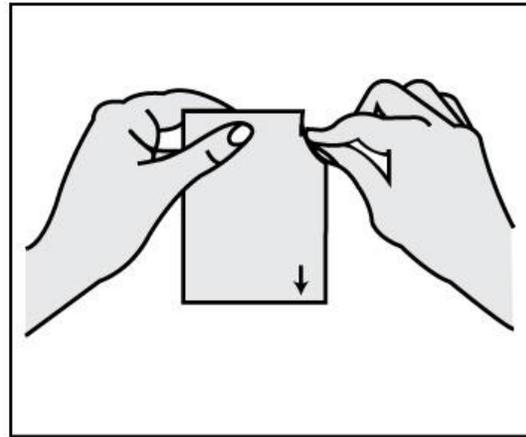


Figure C

Step 2.

- The sticky adhesive side of the patch is covered by 2 strips of overlapping protective liner. **See Figure D.**
- Remove the first piece of the protective liner and place the patch, adhesive face down, firmly onto the skin. **See Figure E.**

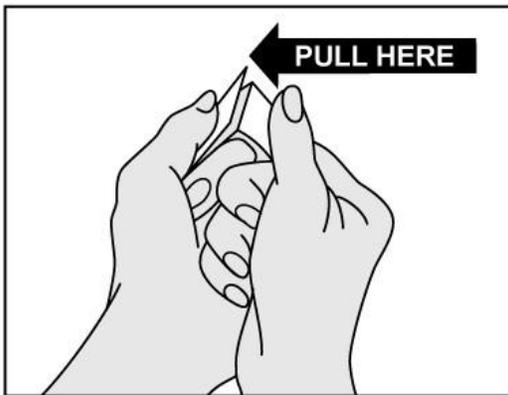


Figure D

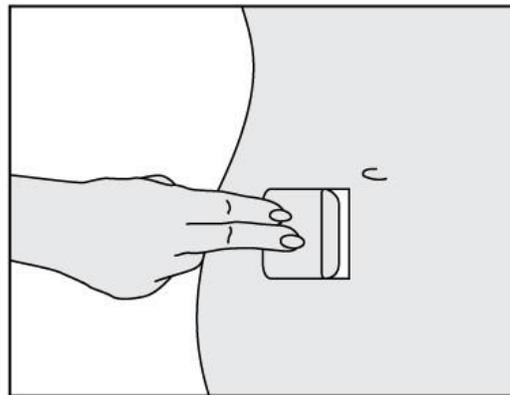


Figure E

Step 3.

- 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 come off the patch. **See Figure F.**
- Apply firm pressure over the surface of the patch with your fingers to make sure the patch stays on. **See Figure G.**
- 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.
- 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. Put on a new patch on a different area of skin, and 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 of skin and continue to follow your original application schedule.

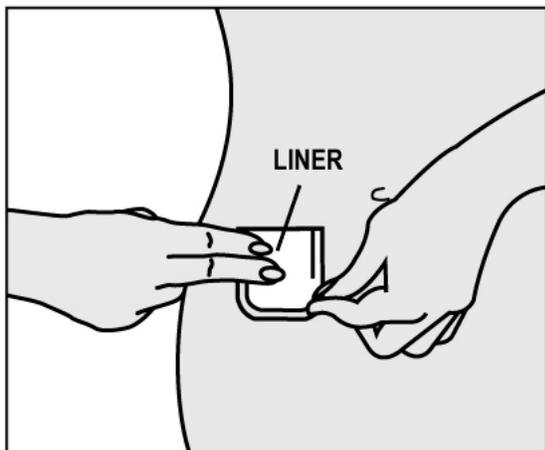


Figure F



Figure G

How to remove OXYTROL:

- When changing your OXYTROL patch, remove the old patch slowly and carefully to avoid damaging your skin.

- After the old patch is removed, fold it in half with the sticky sides together.
- **The patch will still contain some oxybutynin, throw the patch away so that it cannot be worn or swallowed by another person, child, or pet.**
- Gently wash the application site with warm water and a mild soap to 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 adhesive remaining on your skin. 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.

This Patient Package Insert and Instructions for Use has been approved by the U.S. Food and Drug Administration.

For all medical inquiries contact:

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