

**FDA Briefing Document for
Nonprescription Drugs Advisory
Committee**

Oxybutynin Transdermal System

NDA 202211

Proposed Indication:

Treats overactive bladder in women

**Topic: Partial Rx-to-OTC switch for
oxybutynin transdermal system**

Meeting Date: November 9, 2012

Disclaimer Statement

The briefing document contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the over-the-counter switch application for the oxybutynin transdermal system to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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1. Topics for Advisory Committee Discussion

1. Does the totality of the data support that consumers can appropriately self-select to use the oxybutynin transdermal system (TDS) in an over-the-counter OTC setting? Please consider how the study participants in the actual use study who had ineligibilities should be viewed, bearing in mind the safety data from the actual use study.
2. Given that some of the pre-specified endpoints were not met in the LCS, which concepts, if any, are you concerned about in the Label Comprehension Study (LCS) data? If you have concerns, please discuss.
3. The data show that some subjects whose symptoms did not improve or worsened continued using oxybutynin TDS beyond two weeks in order to see if it needed more time to work. Do you have concerns about consumers not stopping use of the product if their symptoms have not resolved?
4. Please discuss any safety concerns about potential delay to diagnosis of conditions with similar symptoms.
5. After you have reviewed the data, we will be interested in your thoughts as to whether the content of the proposed package label is acceptable for OTC marketing.

2. Summary Memorandum

DATE: October 10, 2012

FROM: Andrea Leonard Segal, M.D., Director, Division of Nonprescription Clinical Evaluation

TO: Members, Nonprescription Drugs Advisory Committee (NDAC)

SUBJECT: Briefing document for the oxybutynin transdermal system (TDS)

Introduction:

Thank you for your participation in the upcoming meeting of the Nonprescription Drug Advisory Committee (NDAC) to be held on November 9, 2012. The Advisory Committee on November 9 will be comprised of members from NDAC enriched with some consultants from the Advisory Committee for Reproductive Health Drugs. Attached is the background package for the meeting, which serves as a synopsis for the discussion of issues related to the partial prescription-to-over-the-counter (Rx-to-OTC) switch of the oxybutynin TDS.

FDA approved oxybutynin TDS as a prescription product in Feb, 2003, for “the treatment of overactive bladder with symptoms or urge urinary incontinence, urgency, and frequency.” The active ingredient is oxybutynin, a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. Oxybutynin relaxes bladder smooth muscle, increasing both urinary bladder capacity and the volume to first detrusor contraction. The prescription product is approved for both men and women. The average daily dose of oxybutynin absorbed from the transdermal system is 3.9 mg. Each system is worn on the skin for four days.

The proposed OTC use is "treats overactive bladder in women." By confining the OTC indication to women, the issue of delayed diagnosis of prostate disease is obviated. The data discussed will include a summary of the postmarketing experience with the oxybutynin TDS, and the results of consumer studies, including label comprehension studies, self-selection studies, and an actual use study. The committee will be asked to consider whether the data support that the oxybutynin TDS can be used appropriately and safely by OTC consumers.

Summary of Briefing Package Contents:

The briefing package contains the following information:

- A general overview of the types of consumer studies that are often performed to support the switch of a prescription drug to OTC marketing. The types of studies described are label comprehension studies, self-selection studies, and actual use

studies, all of which were performed to support the application under consideration.

- An overview of the data that supported the original FDA approval of Oxytrol Transdermal System (TDS). This section includes background information about overactive bladder and treatment options.
- An overview of the results of the label comprehension and self-selection studies, with a particular focus on the pivotal label comprehension study, used to support the application.
- A summary of the results of the actual use study the Consumer Trial of Oxytrol (the CONTROL study)
- A summary of the safety profile of oxybutynin TDS from the CONTROL study, postmarketing studies, and postmarketing report databases. Also included in this section is a discussion of specific safety issues of interest.

Finally, the three Appendices include copies of the current prescription labeling, the proposed OTC labeling, and the label used in both the pivotal label comprehension study and the actual use study.

FDA Issues or Questions: The issues for discussion are identified in Section 1. Topics for Advisory Committee Discussion. After you have reviewed the data, we will be interested in your views as to whether the content of the proposed package label is acceptable for OTC marketing.

Conclusion Statement:

In the OTC setting, consumers must be able to understand the product label, self-diagnose a condition, make a self-selection decision (determine whether a product is appropriate for their personal use for the condition) and use the product appropriately based upon the product labeling. OTC drug products should have a favorable safety profile. In accordance with FDA regulations, if a drug can be OTC, it should be OTC. It will be important for you to bear these things in mind as you study the background packages and as you listen to the presentations at the Advisory Committee Meeting on November 9, 2012.

During the meeting, we hope to gain insight to help us decide whether the totality of the clinical and consumer data demonstrate that the risk/benefit profile of oxybutynin TDS is favorable to support the OTC availability of this product. We will not be re-visiting the risk/benefit determination for Oxytrol in the prescription setting. The information on the condition of overactive bladder, the safety data from prescription use, and the consumer studies are provided to inform the discussion of this proposed Rx-to-OTC switch. We anticipate a very interesting and productive meeting.

3. Overview of Consumer Studies that May Support an Rx-to-OTC Switch

A consumer who uses an OTC product is making his or her own healthcare decision without a healthcare provider intermediary. Consumer studies can support OTC approval of a drug product by showing that consumers are able to understand the product label and can appropriately self-select, and self-medicate for a particular condition in an OTC environment using only the OTC drug label.

This overview will summarize the general characteristics of three types of consumer behavior studies, Label Comprehension Studies (LCS), Self-Selection (SS) and Actual Use Studies (AUS). Data from these studies provide information about how well an over-the-counter (OTC) product label can inform the nonprescription drug consumer about the drug and whether the consumer can appropriately use the information on the label. Thus, these data play a major role in helping to determine whether a product should be marketed without a prescription.

The prescription to OTC switch process is guided by federal regulations. The Federal Food, Drug, and Cosmetic Act Sec. 201. [321] (g)(1) states that the term “drug” means articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease and intended to affect the structure or any function of the body of man. The Durham-Humphrey Amendment to the Federal Food, Drug, and Cosmetic Act draws a distinction between prescription and non-prescription drugs. This distinction is stated in the Code of Federal Regulations 21 CFR 310.200(b) as follows:

“Any drug limited to prescription use under section 503(b)(1)(C) of the act shall be exempted from prescription-dispensing requirements when the Commissioner finds such requirements are not necessary for the protection of the public health by reason of the drug’s toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and he finds that the drug is safe and effective for use in self-medication as directed in proposed labeling.”

When a drug that has been previously available only by prescription is switched to OTC status, the healthcare provider is no longer a gatekeeper to drug access. Thus, drug labeling must communicate directly to the consumer. The consumer must understand and act appropriately based on the information available in OTC labeling.

While the general structure of the OTC drug label is codified in the Code of Federal Regulations, the text used to communicate to consumers undergoes iterative study and optimization. (See Appendix 2 – Proposed Nonprescription Labeling for oxybutynin TDS, for an example of a “Drug Facts” OTC label.) Labeling used in LCS, SS, and AUS studies evolves, and the final product labeling ideally reflects the lessons learned from consumers following a careful label development program.

The development program for oxybutynin TDS was an iterative process that involved LCS, SS, and AUS. Proposed labeling for oxybutynin TDS includes the principal display panel and Drug Facts section required by regulation. (See Appendix 2 – Proposed Nonprescription Labeling.)

Label Comprehension Studies (LCS):

It is important to study whether consumers can understand the information on a product label, particularly when new OTC indications, directions for use, and new warnings are contained therein. LCS can help to develop labeling that communicates effectively.

The study is a critical element to the label development process for an OTC drug. If a study succeeds, it can at least assure that respondents understand the label that is used in the Actual Use Study, and this label will be similar, if not identical, to the label that accompanies the product to market. If the results suggest that certain elements are not understood, the study can still be contributory as long as information is collected to help establish the reasons for the errors. The LCS results may not accurately predict consumer behavior, such as self-selection, purchase decisions, or adherence. (It is important to note that, for the oxybutynin TDS application, the sponsor conducted the pivotal LCS and the AUS simultaneously using the same label; therefore, the label used in the AUS did not reflect information derived from the pivotal LCS.)

LCS should have a series of key communication objectives, (the information that it is important to convey to the consumer). LCS can test how well consumers comprehend the information displayed on the outside of the drug carton, contained inside the package (inserts), and any other crucial informational material. The investigators should ascertain why participants who answer incorrectly, answer the way they do so that this information can improve the label. The label development process is ideally an iterative one. If the tested label does not communicate the important medical messages adequately, the labeling can be revised and another LCS performed.

Label comprehension studies can be useful under many different circumstances, including the following, all of which apply to the oxybutynin TDS switch to OTC:

- The drug is the first in its class to enter the OTC market;
- The drug targets a new OTC population;
- There is a new OTC indication.

Study Design:

The label comprehension study is a study in which no drug is administered. Study participants (respondents) read the label to be tested. Trained investigators administer a questionnaire (the study instrument) using scripted interactions with the respondent. Generally respondents are given unrestricted time to read the label and can refer back to it during the testing. The purpose of the testing is to assess comprehension, not memorization.

Target Population:

We try to obtain an LCS target population that is representative of the United States population of potential product users and nonusers. To attract this target population, tests have been administered in shopping malls and other purchase sites that are demographically diverse.

The general population is often enriched with subgroups of special interest, for example, those of a particular gender, age, race, sex, or those with a medical condition that would put them at high risk if they took the drug. The populations have included a low literacy cohort, generally identified by the score on the Rapid Estimate of Adult Literacy in Medicine (REALM) test. This test was used to identify low literacy cohorts for the Oxytrol TDS consumer studies.

Questionnaire:

The main data collection tool for a LCS is the consumer Questionnaire. The questionnaire should be designed to reflect the communication objectives of the study. The wording of the questionnaire, the order of questions, and the structure of the questions can affect the results of the study by not gathering the appropriate information, introducing respondent fatigue, or by introducing bias.

There are many types of questions that have been used and each has advantages. Open-ended questions allow the respondent to give an unrestricted answer that can be recorded verbatim. Closed-ended questions offer the opportunity for the respondent to choose from among a restricted answer set as in a multiple choice question. Scenarios are questions that require the respondent to apply information from the label to respond correctly. A scenario question consists of a brief description of a medical situation. The respondent responds to a question about whether, in this situation, the product would be appropriate to use. Scenario questions can provide very informative data and may offer a window into the ability of respondents to use the product properly. They are being used commonly in LCS because they require not just the comprehension of information, but the ability to process it.

Information from one question should not influence the responses to subsequent questions. It is important that multiple choice questions be mutually exclusive and that they not contain language that participants may interpret as a “safe” answer. They should not contain a default answer such as “ask a doctor” unless asking a doctor is the correct answer according to the label.

Analysis:

It is important to note that adequate label communication is an issue of clinical judgment and varies depending upon the medical significance of a particular communication objective. Different healthcare professionals may have different thresholds for adequacy and thus this often has become a matter of discussion.

Results for each communication objective have been analyzed by the general population and by specific subgroups to determine the percentage of correct responses. We often make a decision based on the lower bound of the 95% confidence interval around the point estimate of correct responses for comprehension. Typically, this point estimate is compared with a pre-specified target threshold for success that is supported by a clinical rationale. Determining pre-specified targets for success is difficult and not a very rigorous scientific process.

It is common that the low literacy cohort (those who read at less than an eighth grade level) does not perform as well as the normal literacy cohort. You will see that this was true for the Oxytrol TDS consumer data. Determining what is an acceptable difference in label comprehension between the normal and low literacy cohorts is a challenge.

Self-Selection Studies (SS):

Self-selection data are collected to determine if a consumer can, after reading the product label, make a correct decision about whether or not the product is appropriate for him/her to use based upon the indications and warnings. SS should assess the ability of a consumer to correctly self-diagnose the condition for which a product is indicated and determine whether the product is appropriate for them to use. No drug is administered during a self-selection study. Sometimes self-selection data are collected as part of an actual use study, sometimes as part of an LCS study and sometimes as a stand alone study. For the Oxytrol application, three self-selection studies were conducted and self-selection information was also available indirectly from an actual use study (see below) related to purchase decisions that study participants made. Self-selection was not a primary or secondary endpoint in the actual use study.

Study Design:

The target population of the SS should be potential users of the product some of whom could use the product and some of whom should not use the product. Study participants review the product label and are asked a self-selection question to which they respond. In one self-selection study for the oxybutynin TDS application, the self-selection question was, “Do you feel that this product is right for YOU to use?” Validating the self-selection response is important. Clearly, it is important to understand why consumers self-select incorrectly. Alternatively, perhaps what appears to be an error is really medically acceptable for the individual and mitigation can be considered in the analyses based upon this circumstance. Other areas that need attention with regard to the self-selection study design are:

- The best wording for posing the self-selection question so it will not influence how people may respond to it;
- The appropriate way to assess self-selection in subpopulations at risk for using the drug.

The acceptability of the success rate for pivotal issues related to self-selection for an OTC product and the acceptability of the failure rate is often the topic of debate. For example,

when should the majority who could benefit from access to an OTC drug be denied that access because of self-selection errors made by a small subpopulation that could be at risk for using the drug? How significant are the clinical consequences of not heeding a specific labeling message?

Analysis:

SS typically provide a point estimate and a 95% confidence interval around the point estimate of correct response for self-selection. The calculation of the point estimate is pre-specified in the protocol, and the acceptable target threshold is ideally supported by a sound clinical rationale. Interpreting data when multiple selection criteria are required for correct self-selection can be complicated.

Actual Use Studies (AUS):

In an actual use study participants actually take the study drug home and may use it, so, unlike an LCS or SS, an AUS is a clinical trial. The purpose of an actual use study is to simulate the OTC use of a product. Hopefully, the AUS can provide meaningful consumer data so we can attempt to predict if a drug will be used properly, safely, and effectively in the OTC setting. Examples of things an actual use study can assess are:

- Adherence (taking the drug and performing any monitoring for efficacy and safety in accordance with the drug label);
- Safety (adverse events that occur during the study);
- Efficacy (whether the clinical benefit in the prescription setting is reproduced in the OTC setting). This seldom has been done (and was not done for oxybutynin TDS).

AUS can assess the ability of the consumer to use the product for the indicated purpose (self-treat) and can also assess whether consumers are abusing or misusing, the study drug. Some issues that might trigger the need for an actual use study include:

- New OTC indication;
- New method of use for an OTC drug;
- New OTC warnings;
- New OTC medical follow-up requirements or recommendations;
- Specific concerns about self-selection or de-selection.

Study Design:

The design of an AUS can vary. Usually AUS have been single-arm, multi-center, uncontrolled, open-label studies (the oxybutynin TDS CONTROL study is an example of this design). An AUS should be performed in a venue that simulates, as closely as possible, the true OTC environment. It is clear that a truly “naturalistic” environment cannot be perfectly achieved; data need to be collected. However, if no clinical sites are used, if the study participant can purchase study drug without restriction, and if there is no unsolicited healthcare provider involvement, a study can come close to simulating a real nonprescription purchase setting. Study elements that limit the naturalistic setting are the informed consent form, data collection tools like diaries which can serve as memory

prompts to the study participant, and any other educational tools that may not be carried over into the true OTC setting. When study elements that limit the naturalistic setting are used in the AUS we cannot be certain that the same level of safety and efficacy will be achieved if the consumer uses the product without these additional elements. This issue is always considered when we provide comments to a sponsor about their AUS study design.

Ideally, all consumers who have an interest in the product should be the target of recruitment efforts. It is also reasonable to recruit targeted subgroups of interest (e.g., low literacy, specific demographics, and medical conditions). These subgroups can provide more information about the potential safety (or efficacy) concerns.

We grapple with what an acceptable success rate is for pivotal issues related to actual use for an OTC product. Acceptable error depends upon the specific drug, specific indication, and safety concerns. Consideration needs to be given to how we should make decisions on approval of a drug when a small percentage of users could potentially be harmed by inappropriate use, but, on the other hand, a large percentage of users may benefit.

Analysis:

The number of study participants enrolled has varied with each drug and situation. Among the factors that could influence the number would be the incidence of the condition, the drug risks, and the cohorts. As with the LCS and SS, data have been presented for AUS as a point estimate of correct response. The point estimate is compared to a pre-specified target threshold, whose acceptability should be supported by a sound clinical rationale.

4. Overview of the Drug Development Program for the Prescription Approval (NDA 21-351): Oxybutynin Transdermal System (TDS)

Background Information

Introduction

Oxybutynin Transdermal System (proprietary name, Oxytrol) is an anti-muscarinic dermal patch that contains oxybutynin and was initially approved as a prescription product in 2003. Oxybutynin transdermal system (TDS) is indicated for the treatment of overactive bladder. It is applied twice-weekly to dry, intact skin on the abdomen, hip or buttock. Oxybutynin is also available as a prescription product in oral and transdermal gel formulations.

Definition of Overactive Bladder

Overactive bladder (OAB) as defined in 2002 by the International Continence Society is a symptom complex that includes urinary urgency, with or without urgency incontinence, associated with urinary frequency and nocturia, in the absence of other local or metabolic factors that would account for the symptoms.

Urgency is the most prominent feature of OAB, and is defined as a sudden compelling desire to urinate that is difficult to defer. OAB is a diagnosis that is based on clinical symptoms and there is no physical finding or laboratory result that establishes the diagnosis.

Epidemiology

OAB is a chronic problem in both men and women with fluctuating severity of symptoms. A European study (the EPIC study) has estimated the prevalence of OAB at 11.8%¹. In this study prevalence increases with age, but was broadly similar in men and women. Another study of a US population (the NOBLE study) has shown a higher prevalence rate of around 16%².

OAB has a negative effect on quality of life, even after controlling for co-morbidities. Patients limit their fluid intake, avoid sexual intimacy, and have to wear pads. There is an increased risk of being injured in a fall and of fractures in older people with OAB compared to those without OAB³.

¹ Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006;50(December (6)):1306–14

² Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003;20(May (6)):327–36.

³ Brown JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. *J Am Geriatr Soc* 2000;48(July (7)):721–5.

It is estimated that OAB results in healthcare costs to developed nations of billions of dollars per year⁴. The largest cost driver is the purchase of incontinence pads, followed by physician visits. The economic burden of OAB will increase, given the demographic shift of an aging population, coupled with the increased prevalence of OAB with age.

Pathophysiology

The etiology of OAB is unknown. There is known to be a familial association⁵. Other factors that have been associated with OAB include obesity, smoking, and consumption of carbonated and caffeine containing beverages.

Normal lower urinary tract function is controlled by the central nervous system (CNS). During the urinary storage phase there is detrusor relaxation and outlet closure. The voiding phase is a reversal of the storage phase with detrusor contraction and bladder outlet relaxation. The brainstem regulates the coordination between detrusor and bladder outlet. Delivery of the CNS signals is relayed through the peripheral autonomic (sympathetic and parasympathetic) nervous system and somatic innervation. Sensory innervation is crucial in enabling the CNS to monitor the state of bladder filling. Within the bladder wall, several mechanisms contribute to key aspects of storage, voiding, and generation of afferent information. Dysfunction at any level of this complex hierarchy of mechanisms can cause bladder dysfunction and resultant symptoms.

Diagnosis

Overactive bladder consists of irritable voiding symptoms that occur “in the absence of other local or metabolic factors that would account for the symptoms.” There is no specific symptom, physical finding, or laboratory value that can establish the diagnosis. Rather, the diagnosis is made by excluding other causes in patients having symptoms compatible with the condition - urgency (with or without urge incontinence), frequency, and nocturia.

Conditions that can cause symptoms similar to those of OAB include urinary tract infection, bladder malignancy, uncontrolled diabetes mellitus, pregnancy, prostate disease, pelvic relaxation, fecal impaction, urinary retention with overflow, and other neurological and endocrine diseases

Treatment - Initial

An International Consultation on Incontinence⁶ has published an algorithm that suggests that the initial treatment for this condition should be a conservative one and that pharmacological measures or device based treatments should follow if conservative

⁴ Reeves P, Irwin D, Kelleher C, et al. The current and future burden and cost of overactive bladder in five European countries. *Eur Urol* 2006;50(November (5)):1050–7.

⁵ Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. *BMJ* 2004;329(October (7471)):889–91.

⁶ Abrams P, Andersson KE, Birder L, et al. Fourth International Consultation on Incontinence Recommendations of the International Scientific Committee: evaluation and treatment of urinary incontinence, pelvic organ prolapse, and fecal incontinence. *Neurourol Urodyn* 2010;29(1):213–40.

measures are not sufficiently helpful. Treatment should be initiated in patients who are sufficiently bothered by their symptoms to seek assistance.

Conservative measures that are initiated in clinical practice include limitation of fluid intake and avoidance of caffeinated and carbonated beverages. Bladder training can be attempted. This training aims to extend the time between voids and in this manner re-establish better inhibitory influences. Bladder training does not have a strong scientific basis but has been shown to have some benefit in the published literature⁷.

Treatment - Pharmacologic

Antimuscarinic (anticholinergic) drugs have been the mainstay of pharmaceutical management of OAB, competitively inhibiting either all detrusor muscarinic receptors, or by competitively inhibiting one specific muscarinic receptor, known as M3. This inhibition of the detrusor muscarinic receptors results in an inhibition of the receptor-mediated detrusor contractions with a resulting improvement in irritable voiding symptoms.

Several marketed agents are available. A report from the International Consultation on Incontinence concluded that the currently used drugs in this class are efficacious with an acceptable tolerability and safety profile⁸. None of the sponsors of these OAB products have submitted evidence to the Agency that establishes one drug product in this class as superior within the class. Table 1 shows currently approved anti-cholinergic drugs for OAB:

⁷ Wallace SA, Roe B, Williams K, Palmer M. Bladder training for urinary incontinence in adults. Cochrane Database Syst Rev 2004;(1):CD001308.

⁸ Andersson KE, Chapple CR, Cardozo L, et al. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. Curr Opin Urol 2009;19(July (4)):380–94.

Table 1. Available Anti-Cholinergic Products Indicated for Treatment of OAB

Active Ingredient	Trade Name	Dose/Formulation	NDA	Approval Date
Oxybutynin	Ditropan XL	Extended Release Tablet, 5mg, 10mg, 15mg	20-897	December 1998
	Oxytrol	Transdermal Patch, 3.9 mg/day	21-351	February 2003
	Gelnique	Transdermal Gel 10%, 100mg Packets	22-204	January 2009
	Anturol	Transdermal Gel 3%, Metered Dose Pump	202-513	December 2011
Solifenacin	Vesicare	Oral Tablet 5mg, 10mg	21-518	November 2004
Darifenacin	Enablex	Extended Release Tablet 7.5mg, 15mg	21-513	December 2004
Fesoterodine	Toviaz	Extended Release Tablet 4 mg, 8mg	22-030	October 2008
Tolterodine	Detrol	Oral Tablet 1mg	20-771	March 1998
	Detrol LA	Extended Release Tablet 2mg, 4mg	21-228	December, 2000
Trospium	Sanctura	Oral Tablet 20mg	21-595	May 2004
	Sanctura XR	Extended Release Capsule 60mg	22-103	August 2007

In addition to the above antimuscarinic drug products, a beta-3-adrenoceptor agonist, Myrabetriq (mirabegron), was approved by the FDA in June 2012 for treatment of OAB. The primary mechanism of action of mirabegron is to relax detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle resulting in increased bladder capacity.

Treatment – Device Based

Patients with significant symptoms refractory to pharmaceutical treatment may be treated with a sacral nerve stimulator device (InterStim®). The basis for treatment using this device is modulation of local reflex control of the lower urinary tract through continuous low level stimulation of the sacral nerves. This device was approved by the FDA for treatment of the symptoms of OAB as well as for treatment of other urinary and lower bowel conditions. This treatment requires the implantation of a sacral nerve stimulator under anesthesia.

Conclusions

Overactive bladder (OAB) is a common disorder in the US, more prevalent in the elderly and those with co-morbid conditions such as diabetes, with a substantial negative effect on quality of life. OAB is diagnosed by excluding other local bladder disease or neurological or endocrine conditions that can cause similar symptoms. Currently there is no cure for OAB, and treatment, including use of oxybutynin TDS, is aimed at providing symptomatic relief.

Major Safety-Related Sections in the Oxytrol Label

Oxytrol currently has the following class-related **Contraindications** in the product label:

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

Oxytrol currently has the following class-related **Warnings and Precautions** in the product label

- Urinary Retention: Use caution in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.
- 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.
- Central Nervous System Effects: Somnolence has been reported with OXYTROL. Advise patients not to drive or operate heavy machinery until they know how OXYTROL affects them.
- Angioedema: Angioedema has been reported with oral oxybutynin use. If symptoms of angioedema occur, discontinue OXYTROL and initiate appropriate therapy.
- Skin Hypersensitivity: Discontinue OXYTROL in patients with skin hypersensitivity.
- Use with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

Oxytrol (oxybutynin) Transdermal System – Efficacy Database Supporting Approval

Efficacy of Oxytrol (oxybutynin) Transdermal System (TDS) was established based on results of 2 clinical trials submitted to NDA 21-351. An overview of the pivotal phase 3 trials is outlined in Table 2.

Table 2. Overview of Phase 3 Trials for Oxytrol

Trial Number	Design & Control Type	Treatment Duration	Arms	Primary Endpoint
O99009	Randomized 1:1:1:1, Double-blind, parallel	12 Weeks	Placebo (n=127) Oxybutynin TDS 1.3 (n=127), 2.6 (n=128), 3.9 (n=120) mg/day	Change in mean urinary incontinence episodes/week
O00011	Randomized 1:1:1, Double-blind, parallel	12 Weeks	Placebo (n=117), Tolterodine 4 mg (n=123), Oxybutynin TDS 3.9 mg/day (n=121)	Change in mean urinary incontinence episodes/day

Trial O99009

Design

This trial included a screening period of 3 to 4 weeks followed by a 12-week, randomized, double-blind, placebo-controlled treatment period. Subjects who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm², 26 cm², or 39 cm² Oxybutynin TDS, or placebo TDS. The active patch delivered a nominal dose of 0.1 mg oxybutynin/cm² surface area per day. Hence, the 13, 26 and 39 cm² patches delivered nominal daily doses of 1.3, 2.6, and 3.9 mg oxybutynin, respectively. The placebo TDS was identical to the active patch, but contained no active ingredient.

This trial included three periods for a total trial duration of 1 year:

- (1) A 12-week, double-blind, placebo-controlled period evaluating three doses of Oxybutynin TDS, followed by;
- (2) A 12-week, open-label, dose-titration safety period, and;
- (3) A 28-week, fixed-dose, open-label uncontrolled safety extension

All subjects who completed the 12-week double-blind period were then eligible to enter the 12-week, open label, dose-titration safety period. The subjects who completed the 12-week open-label safety period were eligible to enter the open-label safety extension. The objective of this period was primarily to acquire additional safety data on use of the oxybutynin TDS.

The primary efficacy endpoint during the double-blind period was the change in average number of urinary incontinence episodes per week from baseline to end of treatment.

Secondary endpoints included change from baseline for urinary frequency and urinary void volume.

Demographics

Subjects participating in trial O99099 were primarily elderly Caucasian women with a lengthy history of symptoms of overactive bladder. The enrolled population included both men and women of Caucasian, Black, Asian/Pacific Islander, and Hispanic ethnicity. Patient age ranged from 20 to 88 years. Subject demographics reported in the 12-week open-label safety period were similar to those for the double-blind period and are presented in Table 3.

Table 3. Demographic and Baseline Characteristics – Trial O99099 Open Label Period

Characteristic	Oxybutynin TDS ¹							
	13 cm ² n = 13		26 cm ² n = 54		39 cm ² n = 75		Overall n = 142	
	n	%	n	%	n	%	n	%
Gender								
Female	8	61.5	52	96.3	70	93.3	130	91.5
Male	5	38.5	2	3.7	5	6.7	12	8.5
Race								
Caucasian	11	84.6	49	90.7	68	90.7	128	90.1
Black	1	7.7	3	5.6	4	5.3	8	5.6
Asian/Pacific Islander	1	7.7	0	0.0	0	0	1	0.7
Hispanic	0	0	2	3.7	3	4.0	5	3.5
Age (years)								
Mean ± SD	62.8 ± 13.3		63.0 ± 10.7		62.1 ± 12.3		62.5 ± 11.7	
Range	36-76		41-84		23-84		23-84	
Duration of incontinence (months)								
Mean ± SD	105.3 ± 144.0		112.5 ± 108.5		145.2 ± 157.2		129.1 ± 139.5	
Range	7-480		12-600		6-720		6-720	

Source: NDA 21-351. Clinical Review Table 2 page 33.

Subject Disposition

A total of 520 subjects who met enrollment criteria during the screening period entered the trial of which 447 completed the double blind phase. Four hundred and eleven subjects entered the 12-week open-label phase, and 142 entered the subsequent 28-week extension.

Subjects enrolled at trial site number 12 were excluded from the final trial analysis, as recommended by the Division of Scientific Investigation, due to data collection/reporting irregularities identified at the site.

Efficacy Results

Trial O99099 did not demonstrate significant efficacy for the 1.3 mg/day and 2.6 mg/day doses. Table 4 shows the results for the 3.9 mg/day dose as compared to placebo.

Table 4. Efficacy Results of Trial O99009

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**	

Source: Oxytrol approved labeling

*Comparison significant if $p < 0.05$

**Comparison significant if $p \leq 0.0167$

Efficacy Conclusions

The review team concluded that oxybutynin TDS 3.9 mg/day:

1. Demonstrated statistically significant improvement compared to placebo in reducing the mean number of weekly incontinence episodes (-21 for drug, -19.2 for placebo),
2. Demonstrated statistically significant reduction in the mean number of daily micturition episodes (-2.2 for drug, -1.6 for placebo)
3. Demonstrated statistically significant increases in the average urinary volume per void (+31.6 mL for drug, +10.5 mL for placebo).

Trial O00011

Design

This was a multicenter, double-blind, 3-arm trial comparing safety and efficacy of oxybutynin TDS with tolterodine oral treatment and placebo in subjects who had achieved a beneficial response from current pharmacological treatment for OAB. The primary endpoint was the change in average number of daily urinary incontinence episodes. The secondary endpoints were the same as those evaluated in trial O99009.

The trial included a screening period of 3 to 4 weeks followed by a 12-week treatment period. Screening consisted of a 2-week washout from current overactive bladder treatment, practice of bladder and fluid management techniques, and completion of a 3-day urinary diary at the end of the 2-week screening period. Subjects who met the eligibility criteria then received one of three randomized treatments: 39 cm² oxybutynin TDS (3.9 mg/day) plus placebo capsules, 4 mg tolterodine long-acting capsules plus placebo TDS, or placebo treatment (capsules and TDS). Transdermal systems were applied twice weekly (every 3-4 days) to the abdomen and capsules taken orally once daily throughout the 12-week treatment period.

A total of 361 subjects were enrolled in the trial of which 320 completed the trial. At the end of the 12-week treatment period, 284 subjects entered a 12-month open-label uncontrolled extension trial and were treated with twice weekly Oxybutynin TDS.

Demographics

Subjects participating in trial O00011 were primarily elderly Caucasian women, although the trial included both men and women of Caucasian, Black, Asian/Pacific Islander and Hispanic ethnicity. The mean age of subjects was 63.5 ± 12.6 years. The treatment groups were balanced with respect to other physical characteristics such as height, weight, and body mass index; general medical history; urinary history; and current pharmacological treatment for overactive bladder.

Table 5. Demographic and Baseline Characteristics – Trial O00011

Characteristic	Placebo N = 117		Tolterodine N = 123		Oxybutynin TDS N = 121		Overall N = 361	
	n	%	n	%	n	%	n	%
Gender								
Female	109	93.2	117	95.1	109	90.1	335	92.8
Male	8	6.8	6	4.9	12	9.9	26	7.2
Race								
Caucasian	110	94.0	120	97.6	111	91.7	341	94.5
Black	4	3.4	1	0.8	8	6.6	13	3.6
Asian/Pacific Islander	0	0.0	0	0.0	1	0.8	1	0.3
Hispanic	3	2.6	2	1.6	1	0.8	6	1.7
Age (years)								
Mean ± SD	64.5 ± 12.3		62.9 ± 13.5		63.1 ± 12.0		63.5 ± 12.6	
Range	29-87		18-85		26-89		18-89	
Duration of incontinence (months)								
Mean ± SD	130.8 ± 136.9		108.6 ± 121.2		101.5 ± 105.5		113.4 ± 122.0	
Range	6-768		8-648		4-516		4-768	

Source: NDA 21-351. Clinical Review Table 5 page 43

Subject Disposition

Of the 733 screened subjects, 361 were enrolled and randomized at 48 sites: 121 (33.5%) to receive 3.9 mg/day Oxybutynin TDS, 117 (32.4%) to receive placebo and 123 (34.1%) to receive 4 mg tolterodine long-acting capsules. The primary reason for not qualifying was failure to meet the required frequency of incontinence episodes (108), followed by subject decision not to participate (90). Three hundred and twenty (88.6%) of the 361

subjects completed the double-blind period. Of the 41 (11.4%) subjects who discontinued early from the trial, 23 withdrew due to adverse events, 14 due to subject decision to withdraw, 3 due to protocol violations and 1 was lost to follow-up.

Overall compliance was over 90% throughout the trial, and was similar for the three treatment groups. Mean compliance for TDS application ranged from 91.4% to 93.2% at endpoint, with an overall compliance of 92.2%. There were no differences in compliance for subjects receiving active versus placebo TDS systems. Mean compliance for capsule administration ranged from 90.8% to 93.7% at endpoint.

Efficacy Results

Table 6 shows the results for Oxytrol as compared to the results for placebo for the primary and key secondary endpoints.

Table 6. Efficacy Results of Trial O00011

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*	

*Comparison significant if $p < 0.05$

Source: Oxytrol approved label

Efficacy Conclusions

The review team concluded that oxybutynin TDS 3.9 mg/day:

1. Demonstrated a statistically significant reduction as compared to placebo in the mean number of daily incontinence episodes (-2.9 for drug, -2.1 for placebo),
2. Demonstrated a statistically significant increase in average urinary volume per void (+32 mL for drug, +9.3 mL for placebo).

3. Demonstrated an improvement in mean number of daily micturitions, although the difference was not statistically significant.

In Trial O00011 the placebo effect was reasonably large, but oxybutynin TDS demonstrated statistically significant improvements over placebo in reducing incontinence and increasing average void volume. This difference was considered clinically significant as well.

Efficacy Database – Efficacy Conclusions from Trials O99009 and O00011:

Trials O99009 and O00011 demonstrated statistically and clinically significant differences in improving incontinence and increasing the average void volume. In Trial O99009 the improvement in urinary frequency was both statistically and clinically significant. In Trial O00011 there was an improvement in urinary frequency, although it was not statistically different from the change seen with placebo.

These results were considered by the review team to be a satisfactory demonstration of the efficacy of oxybutynin TDS 3.9 mg/day in treating the symptoms of overactive bladder.

Oxytrol (oxybutynin) Transdermal System – Safety Database Supporting Approval

This section provides a brief overview of the safety database provided in the submission of NDA 21-351 for Oxytrol TDS. The dose being considered for OTC use, 3.9 mg/day, is identical to that currently approved as a prescription Oxytrol TDS product.

Safety Database - Demographics and Exposure

The safety profile for the approved prescription Oxytrol TDS product included data from a total of 19 trials. The trials included 16 phase 1 trials, a single phase 2 trial, and two phase 3 trials. The review team evaluated Oxytrol TDS doses that ranged from 1.3 mg/day to 5.2 mg/day. Mean age of the OAB subjects were 62 years (range 18 – 89 years) and 46% were over age 65. Ninety-one percent of the subjects were female and 92% were Caucasian.

Duration of exposure ranged from 1 – 428 days, with an average of 151 days.

Safety Database - Adverse Event Profile

Adverse Events (AEs) were greater in the Oxytrol TDS treated groups (73.0%) compared to placebo (56.6%) groups who used a TDS system without oxybutynin (the active drug substance). Adverse Events which the investigators considered to be related to the treatment were more common in Oxytrol TDS treated subjects (46.6%) than placebo-treated subjects (24.5%) with a trend toward higher incidences of AEs with increasing dose. Key safety findings from the review team included:

- The most common systemic AEs were anticholinergic effects, which was consistent with the known pharmacology of oxybutynin.
- The most common anticholinergic effect reported was dry mouth, occurring in 8.6% of subjects receiving Oxybutynin TDS in both controlled and uncontrolled trials. The incidence of dry mouth was 7.5% for active TDS treatment vs. 5.2% for placebo TDS treatment during controlled trial periods.
- The most common event considered by the investigators to be treatment related was localized skin reactions at application sites, primarily pruritus, occurring in 23.1% of Oxytrol TDS treated subjects.

Other notable safety findings included:

- Application site AEs in subjects treated with Oxytrol TDS were approximately twice that compared to subjects treated with a placebo TDS.
- Application site adverse events were reported by 11.5% of subjects treated from 0-6 weeks, 11.2% treated for 6-12 weeks, 11.2% of subjects treated for 12-24 weeks, and 6.3% for subjects treated for >24 weeks.

Safety Database – Deaths and Serious Adverse Events (SAEs)

The review team identified the following:

- Deaths – There were no deaths during the treatment period in any trial.
 - Two subjects died from non-drug-related causes: heart attack and malignant mixed Müllerian tumor. One death occurred prior to the subject initiating Oxytrol treatment, and the other, following completion of trial participation.
- Serious Adverse Events (SAEs) - A total of 37 subjects experienced a total of 47 SAEs in the 19 submitted trials. None of the SAEs were reported as related to trial drug.
- SAEs were generally of short duration and resolved without sequelae prior to discharge from the trial.
- As a result of the SAEs, 9 subjects discontinued early. The remaining 28 subjects completed the trial according to the dosing regimen. The nine serious events that resulted in discontinuation were
 - Three episodes of chest pain (1 in the 26 cm² group, 1 in the 13 cm² group and 1 in the placebo group);
 - Two episodes of syncope (1 in the 39 cm² group, 1 in the 13 cm² group);
 - One episode of pneumonia with sepsis (13 cm² group);
 - One episode of pancreatitis (39 cm² group);
 - One subject was diagnosed as having a malignant mixed Müllerian tumor which resulted in death 2 months after discontinuation (26 cm² group);
 - One episode of back pain (39 cm² group);
- There were no trends in SAE incidence across different treatment groups.

Safety Database - Discontinuations Due to Adverse Events

The following key safety findings were observed from the reported discontinuations:

- 13.7% of subjects discontinued active TDS treatment due to adverse events; 11.0% discontinued due to events that the investigators considered being treatment related.
- Most of the discontinuations were due to application site reactions. Subjects receiving Oxytrol TDS were more likely to discontinue treatment compared to placebo treated subjects. A trend of increasing discontinuation rate was reported with increasing Oxytrol TDS dose.
- Dry mouth accounted for a discontinuation rate of 0.8%.
- Discontinuation rates tended to decrease with increasing duration of exposure.

Summary of Observed Adverse Events

Table 7 presents the treatment emergent adverse events that occurred in >1% of subjects during the 12 weeks of controlled treatment in the two phase 3 trials.

Table 7. Summary of Adverse Events Seen in >1% of Subjects Treated With Oxybutynin TDS and Placebo TDS during 12 Weeks of Treatment

Preferred Term	Number of Events* (%)	
	Placebo-Containing TDS N=249	Oxytrol TDS 3.9 mg/day N=246
Application Site Pruritus	13 (5.2%)	38 (15.4%)
Application Site Erythema	5 (2.0%)	17 (6.9%)
Mouth Dry	13 (5.2%)	17 (6.9%)
Application Site Vesicles	0	7 (2.8%)
Diarrhea	3(1.2%)	4 (1.6%)
Constipation	0	4 (1.6%)
Dysuria	0	3 (1.2%)
Abnormal Vision	0	3 (1.2%)

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

Source: Oxytrol Approved Label – Compilation of Tables 1 and 2

Safety Database - Overall Conclusions on the Safety Profile:

The safety database for Oxytrol TDS was considered sufficient by the review team for the purpose of approval of the product for the treatment of overactive bladder. The major safety issues identified were related to skin tolerability and anticholinergic side effects such as dry mouth and constipation.

5. Label Comprehension and Self-Selection Studies Summary

Overview of Submitted Studies

The Sponsor has submitted five label comprehension studies and three self-selection studies as part of this NDA submission. The studies are as follows:

- Pivotal label comprehension study– conducted in late 2010:
 - Cohort 1 – females 18 + with self-reported OAB, general population
 - Cohort 2 – females 18+ with self-reported OAB, low literacy enriched,
 - Cohort 3 – females 44+ with self-reported risk of diabetes symptoms
- Label comprehension study with elderly self-reported OAB sufferers – conducted in early 2010
- Label comprehension study of diabetic warnings among general OAB sufferers – conducted in early 2010
- Label comprehension study of enhanced pregnancy warning among women of childbearing age – conducted in early 2010
- Label comprehension study among female OAB sufferers and non-sufferers and men – conducted in 2008
- Self-selection study in pregnant women – conducted in late 2010
- Self-selection study in men – conducted in late 2009
- Self-selection study in women with OAB symptoms; also four other subpopulations: men, diabetics, those with glaucoma; and those pregnant or nursing – early 2009

Label Comprehension Studies: General Comments

The pivotal label comprehension study is the research of the most intense focus here. This is not only because it is the most recent and rigorous research, but also because the other label comprehension studies were more exploratory in nature; moreover, the previous research was based on earlier versions of labels that were subsequently improved as a result of prior consumer research. However, to the extent that there are issues that were not explored in the pivotal LCS, prior relevant research is presented. The label used in the Pivotal LCS can be found in Appendix 3.

Self-Selection Studies: General Comments

The three self-selection studies were not all conducted with the same label as the pivotal label comprehension study. The self-selection study conducted in early 2009 used a label that was markedly different and the unsatisfactory results of this study led to learning that resulted in substantial labeling changes (e.g., highlighted warnings in the Drug Facts label, a pink box, and an icon of a woman on the front of the label (the PDP). The subsequent two self-selection studies (one in pregnant women and one in men) used labels that had those changes.

Approach to Analysis of Label Comprehension and Self-Selection Studies

In approaching this analysis, key issues of concern to FDA were evaluated to determine how the issues fared in the consumer research.

Key Issues of Concern:

- Consumer identification of OAB – can consumers accurately self-diagnose?
- Urinary/gastric retention sufferers – do consumers understand that, if they have been told by a doctor that they have urinary or gastric retention, they should not take Oxytrol?
- Diabetes – do consumers understand that they should ask a doctor before use if they have risk factors or symptoms of diabetes?
- UTI sufferers – do consumers understand that they should not take Oxytrol if they have pain or burning when urinating, blood in the urine, unexplained lower back pain or side pain or urine that is cloudy or foul-smelling?
- Pregnant women – do consumers understand that some symptoms of pregnancy can be similar to some symptoms of OAB, and do they understand that women who know that they are pregnant should ask a doctor prior to taking Oxytrol?
- Men – do consumers understand that men should not take Oxytrol?

Other important issues of concern such as allergy to oxybutynin, kidney stones or liver/kidney disease, narrow angle glaucoma, and ability to correctly use the patch were tested for comprehension in the pivotal LCS study. Results are provided later in this section under Other Medical Issues.

In the pivotal LCS, the Sponsor asked questions regarding comprehension of each of the first 4 Key Issues. According to the Sponsor, predetermined thresholds were established for the first three key issues (listed above) depending on whether they represented relatively high or low medical consequences. Those representing higher medical consequences had a higher bar of success, at 90%. Those representing lower medical consequences had a lower bar of success, at 85%. The Sponsor determined that some questions in the survey, such as those about UTI, were for informational purposes only and did not need to have an associated threshold. The sponsor did not have communication objectives for pregnant women or men in the pivotal LCS. These groups were addressed in the targeted self-selection studies conducted in 2010 in these two populations.

Below are the key medical issues cited above along with the Sponsor's assessment of medical risk for the pivotal LCS:

- Correct OAB self-identification – lower medical risk – 85%
- Urinary/gastric retention – higher medical risk – 90%
- UTI sufferers – pivotal LCS had relevant questions but these were determined by the Sponsor not to be study objectives
- Diabetes – lower medical risk – 85%

Ultimately, label comprehension and self-selection studies can only attempt to measure intended behavior as opposed to actual behavior. How consumers might actually behave is best assessed through an actual use study. The actual use study (the CONTROL study) will be presented and discussed at length in Section 6 of this background package. It is important to note, however, that the actual use study was started in May 2010 and the pivotal label comprehension study was started in October 2010. Therefore, the label used in the actual use study (AUS) was the same that was used in the LCS; the AUS label did not benefit from findings from the pivotal LCS. (As a result of findings from both studies, the Sponsor has revised the label that they propose to bring to market, which can be found in Appendix 2.)

Label Comprehension Studies

Pivotal LCS Methodology:

Cohorts 1 and 2

Cohorts 1 and 2 were conducted with OAB sufferers. In contrast, FDA’s Label Comprehension Guidance for Industry advises that studies should be conducted with “all comers” so as not to upwardly bias results from those already knowledgeable about a condition and existing medications for that condition. The rationale for this is that at any point in time once a product is on the market, there will be new sufferers coming into the target population who need to be able to pick up a label and understand what it says; also, other family members or caregivers may seek to determine, by reading the label on the shelf, whether a product could be used for a family member with the condition.

Cohort 1, n=472, was comprised of a general population of females 18+ with self-reported OAB. A total of 6.2% fell into the low literacy category. Cohort 2, n=120, was comprised of an augmented low literacy sample of females 18+ with self-reported OAB.

The Sponsor based the success thresholds on Cohort 1 alone. Although estimates of the low literacy population can vary widely, 6.2% is quite low and most likely not reflective of the actual percentage of low literates in the general population. Therefore, it is possible that survey results were upwardly biased due to this as well, given that often there is at least directionally – and in some cases significantly - less comprehension among low literacy populations.

Cohort 2, the augmented low literacy sample, was only drawn from 2 sites – making this a not geographically representative sample. Moreover, the age representation in Cohort 2 was very different than Cohort 1. Cohort 1 had 22% of respondents under the age of 34, and Cohort 2 had 42% of respondents under the age of 34.

Cohorts 1 and 2 were asked identical questions, so as to be able to compare the general population with the augmented low literacy sample. Cohorts 1 and 2 were asked questions about the label relating to various topics of medical concern – symptom duration, urinary/gastric retention and foul smelling urine as well as kidney stones, liver or kidney disease, allergy to oxybutynin and the ability to correctly use the patch.

Cohort 3

The objective of Cohort 3 was to examine whether those who were at risk of diabetes understood that OAB symptoms could be masking diabetes onset and that people with specific symptoms should consult with a doctor before using the product. Females 44+ who had not been told by a doctor that they had diabetes or pre-diabetes were eligible to be included in this cohort. To be included, they also needed to report some level of risk for diabetes, which was confirmed through the administration of an online diabetes risk calculator.

Cohort 3 consisted of 160 subjects, with 40% over the age of 60. Unlike Cohort 1, Cohort 3 did not have an associated augmented low literacy sample. The low literacy representation of Cohort 3 subjects was 10%.

Cohort 3 had a different (significantly shorter) questionnaire than Cohorts 1 and 2; the Cohort 3 Questionnaire focused on assessing communication of diabetes messaging. One question covered family history of diabetes, and another covered frequent urination that was accompanied by excessive thirst.

Findings from the Label Comprehension Studies:

The findings discussed below are organized around the key issues of concern outlined above. Unless otherwise stated, the percentages reported below represent the lower bound of the 95% confidence interval, which was calculated and presented by the Sponsor for all of the primary communications objectives as measured against success thresholds of 90% and 85% respectively, depending on the Sponsor's perceptions of medical risk. Occasionally (as when discussing data comparing normal literates to low literates), the percentages represent point estimates. In these cases, the normal literates from the general population cohort are compared with the low literates from both the general population and augmented low literacy cohorts.

Correct OAB Identification

Cohorts 1 and 2 were asked two questions relevant to this issue. Question 3 of the Questionnaire covered a knowledge of the specific symptoms of OAB, and Question 6 was targeted to minimum length of time – 3 months – with which to have the symptoms (which themselves were not listed in the question) prior to initiating therapy. The Sponsor determined that the threshold of success should be applied to the latter question only – dealing with the minimum length of time.

- Consumer understanding from the label that one had to have OAB symptoms for at least three months prior to using the product (Question 6) did not meet the threshold but came within one point of the threshold – at 84%. However; there was a statistically significant difference between normal literates and low literates – 85.2% vs. 67.8%.

- Consumer understanding from the label about specific symptoms (Question 3) scored 84%, with a lower bound of 81%.
- Cohort 3 was also asked the question about specific symptoms (though not the question about symptom duration). That question scored at 86%, with a lower bound of 80%, stating that it was okay to take the product.

Urinary and Gastric Retention

Both urinary and gastric retention scored below, but within five points, of the 90% success threshold in the pivotal LCS. With regard to urinary retention, the lower bound was 88%; with gastric retention, it was 87%. However, there were statistically significant differences in point estimates between normal literacy (NL) and low literacy (LL) subjects, particularly with gastric retention - 87% NL vs. 70% LL. On urinary retention, the difference was 89% NL vs. 75% LL.

UTI

The pivotal LCS had one question about UTI symptoms – referring to foul smelling urine - but the Sponsor did not consider this as a communication objective important enough to be measured against a success threshold. Nonetheless, 88% (lower bound of 84%) of the general population said it was not okay to use. Overall, elderly subjects did not appear to have different significant levels of comprehension than younger subjects. Cohort 3 was also asked the question about foul smelling urine and 86% (lower bound of 79%) said it was not okay to use. There were no questions in the pivotal LCS about any other UTI symptoms such as pain, burning, fever or cloudy urine.

In an earlier LCS with elderly OAB females (n=350), using a slightly different label, the threshold of 90% was exceeded by 4 percentage points (lower bound of 94%) in knowing it was not okay to use if there was blood in the urine, and was exceeded by 3 percentage points (lower bound of 93%) in knowing it was not okay to use if there was pain while urinating. It did not meet the 90% threshold for knowing it was not okay if there was foul smelling urine (lower bound of 88%) or if there was pain in the lower back (lower bound of 89%).

Diabetes

In the pivotal LCS, two diabetes related questions were asked only of Cohort 3 – one relating to family history together with symptoms of frequency/urge of urination and the other relating to frequency of urination and excessive thirst. Both sets of responses did not meet the 85% success threshold, even with sponsor mitigation of the verbatim responses of the respondents.

- History of diabetes – Lower bound 83% - two percentage points below threshold
- Diabetes symptoms – Lower bound 82% - three percentage points below threshold

All subjects in Cohort 3 were asked in screening if they currently were experiencing OAB symptoms; the above diabetes-related comprehension responses did not significantly differ between those who were experiencing the symptoms and those who were not.

It is important to note that although Cohort 3's initial telephone screening involved the diabetes risk assessment calculator, this calculator was re-administered to subjects at the survey site, prior

to the onset of survey administration. While it is common research practice to re-screen subjects at the actual survey site, the impact of administering this particular calculator could have had the effect of reminding and cuing the subjects that diabetes was to be the focus of this survey, therefore potentially upwardly biasing the results.

Other Medical Issues

Below are the results (expressed as the lower bound of the 95% confidence interval) of how other communication objectives determined by the Sponsor to represent higher medical risk (90%) scored in the pivotal label comprehension study:

- Knowledge that it was not okay to use if allergic to oxybutynin – 93% - three percentage points above threshold
- Knowledge of stop use and ask a doctor if there is an allergic reaction to the patch – 91% - one percentage point above threshold
- Knowledge of stop use and ask a doctor if developing blisters and red/itchy rash – 85% - five percentage points below threshold
- Knowledge of not okay to use if have narrow angle glaucoma – 84% - six percentage points below threshold

Below is the result of how other communication objectives determined by the Sponsor to represent lower medical risk (85%) scored:

- Knowledge of ask a doctor if have kidney stones – 87% - two percentage points above threshold
- Knowledge of ask a doctor/pharmacist if using diuretic – 84% - one percentage point below threshold
- Knowledge of ask a doctor if liver disease – 80% - five percentage points below threshold

Self-Selection Studies

Men

The 2010 self-selection study was targeted to 571 men with urinary symptoms. Subjects were given a copy of the labeling to read. Then they were asked, “Do you feel that this product is right for YOU to use?” Then they were asked, “Why do you say that?” Finally, they were asked, “What led you to that decision?”

Correct self-selection scores were 87%, three percentage points below the 90% threshold, with normal literates scoring approximately the same as low literates. Of the men who made an incorrect self-selection decision, 62% focused on the urinary symptoms and not on the language that the product was just for women.

Pregnancy

In 2010, the Sponsor also conducted a self-selection study with 435 pregnant women who had OAB symptoms. Study participants were given a copy of the label to read. Then they were

asked, “Do you believe this product is appropriate for you to use right now, or not?” This was followed with, “Why do you say that?” and then with, “What led you to that decision?”

That study, with a lower bound score of 84% for the general population, failed to meet the primary endpoint of 90%, even with subsequent mitigation based upon verbatim responses. The lower bound score for the low literacy cohort was initially 54%, with mitigation bringing it to 67%.

The majority of those making incorrect self-selection decisions focused on the symptoms the product treats rather than the pregnancy warning on the label. Some also made the point that the label does not say the pregnant woman cannot use the product, but instead that she should talk with her doctor first. Based on the result of this study and additional label research, the female silhouette on the proposed package label has been redrawn to have a narrow waist so she may not be mistaken for being pregnant.

6. Summary of Actual Use Study

This section summarizes the design and endpoint results of the actual use study (AUS) performed to support the NDA application. Section 7 provides a summary of adverse events reported in the AUS.

The AUS is titled the Consumer Trial of Oxytrol (CONTROL; CL2008-13). CONTROL was a phase 3, multicentered, open-label, consumer behavior trial open to all comers to assess use of the oxybutynin patch in a simulated OTC setting. Initial enrollment to completion of the trial lasted from May 2010 – June 2011. Twenty-six pharmacies throughout the United States participated in enrolling subjects and conducting the trial.

CONTROL was a four phase trial:

- Initial screening for recruitment
- Onsite enrollment eligibility assessment
- 12-week use phase
- End-of-study follow-up interview

Objective: Evaluate actual use and outcomes among female subjects who select to use and purchase Oxytrol for Women®. The trial population was designed to represent the planned target OTC population for future marketing.

Recruitment advertising was established to attract women concerned about their OAB symptoms. See **Figure 1** for details of the enrollment process. Screening criteria required that subjects were:

- female
- over 18 years of age
- not pregnant or suspecting of pregnancy
- not trained or employed as a healthcare professional
- not working as a healthcare professional for a pharmaceutical company, pharmacy, managed care or health insurance company. Neither could a household member.
- not participating in market research, label study or clinical trials now or within the prior 12 months.

Male consumers were not targeted via recruitment materials. The words “Attention Women” were at the top of flyers which include images and photos of women only. The flyers were pink. Males who did respond to these materials (n=45; 8% of screened subjects) were excluded from the enrollment and use phases. The sponsor did not collect information from men in this trial about their reasons for considering participation.

Once at the pharmacy site, subjects were asked to view the Oxytrol for Women package and make their own purchase decision. There was no self-selection component of the trial (the trial was not powered to assess the selection decision). Following a decision to

purchase, subjects responded to enrollment interview questions about their OAB symptoms, medical history and demographics.

Then they completed the validated Rapid Estimate of Adult Literacy in Medicine (REALM) test (cutoff < 61 for low literacy) and were assessed as to whether they met exclusion criteria. The sponsor excluded women who

- were pregnant.
- were breastfeeding.
- had a known allergy to oxybutynin.
- had narrow angle glaucoma.
- had hematuria unrelated to menses.
- had back or flank pain with fever and either: hematuria, dysuria or cloudy, foul-smelling urine.

Regardless whether they met criteria, all subjects reported their reasons for purchase decisions. Subjects who signed the Informed Consent, and were not excluded, were invited to enter the use phase of the trial. All subjects, including excluded subjects who had selected to purchase the drug, were asked to provide further Informed Consent to participate in follow up telephone interviews and make medical records available from any physician visits.

Subjects who purchased the product used it based upon their understanding of the Drug Facts label. A diary and follow up interviews at 3, 7 and 12 weeks after initial purchase were used to record patterns of use. “Verified users” were subjects who had recorded using at least one patch in the diary returned to the study coordinator, and had at least one follow up interview. Verified users were the users who were evaluated for the sponsor’s primary endpoint. “Non verifiable users” were subjects who reported using the drug at a follow up interview, but who did not return a diary, or who returned a diary indicating use but who did not complete at least one follow up interview. All of these subjects were included in the safety analysis. Subjects were provided contact information for a healthcare professional available 24 hours per day for the trial duration. Subjects could purchase up to 24 boxes of Oxytrol for Women® over the duration of the trial.

An End-of-Study (EOS) urinalysis was conducted at week 12, or anytime a subject’s participation ended, and a final interview was performed at week 15 when subjects submitted their final diaries. A study pharmacist interpreted the urinalyses results. Subjects who reported misuse were questioned regarding their reasons. Subjects were asked if they consulted a physician at any time during the trial. If so, a study nurse followed up on diagnoses or treatment regimens.

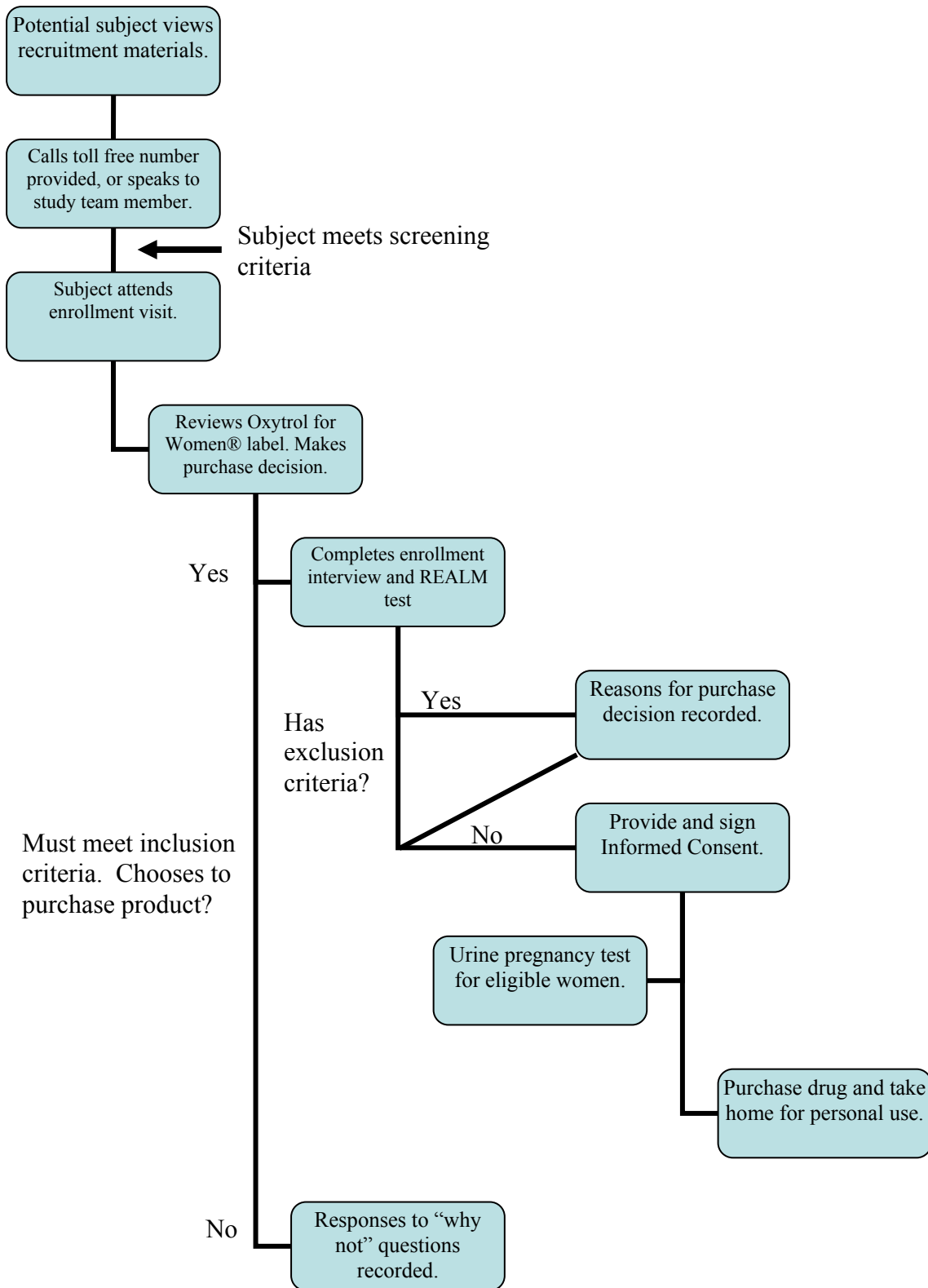


Figure 1: CONTROL Trial Enrollment Diagram
 Created by reviewer

Demographics

As shown in **Table 1**, non-white subjects accounted for nearly 23% of the verified user population. Age ranged from 18 to 94, with adequate means and medians for label evaluators (57.9, 58) and purchasers (58.4, 58). Subjects over age 65 years, and over age 75 years, accounted for 32.7% and 16.6% of the trial population, respectively. Of note, 162 (13.3%) of the label evaluators were determined to be low literate. Somewhat greater percentages of subjects who were black/African American, Hispanic/Latino, high school graduates or had less education, <50 or >80 years of age or low literate were rejected from purchasing the drug compared to verified users of those demographic characteristics. There is no clear explanation for the differences.

Table 1: Demographic Characteristics of Enrollment Population - CONTROL Trial

	Evaluators (N=1218)	Verified Users (N=727)	Rejected from Purchasing (N=214)	Non-purchasers (N=149)
RACE/ETHNICITY				
White	886 (72.7%)	561 (77.2%)	131 (61.2%)	104 (69.8%)
Black/African American	140 (11.5%)	66 (9.1%)	34 (15.9%)	19 (12.8%)
Hispanic/Latino	132 (10.8%)	64 (8.8%)	41 (19.2%)	15 (10.1%)
Asian	18 (1.5%)	12 (1.7%)	1 (0.5%)	4 (2.7%)
Other	42 (3.4%)	24 (3.3%)	7 (3.3%)	7 (4.7%)
EDUCATION				
8 th grade or less	17 (1.4%)	9 (1.2%)	4 (1.9%)	3 (2.0%)
Some high school	74 (6.1%)	35 (4.8%)	15 (7.0%)	14 (9.4%)
High school graduate/GED or certificate	330 (27.1%)	178 (24.5%)	70 (32.7%)	41 (27.5%)
Some college/technical school	454 (37.3%)	283 (38.9%)	74 (34.6%)	48 (32.2%)
College graduate	250 (20.5%)	165 (22.7%)	36 (16.8%)	31 (20.8%)
Post-graduate degree	93 (7.6%)	57 (7.8%)	15 (7.0%)	12 (8.1%)
AGE DISTRIBUTION				
Mean (SD)	57.9 (15.7)	58.4 (15)	56.1 (16.7)	61.2 (16.8)
Median	58	58	56	61
Range	18-94	18-94	18-92	18-92
AGE GROUPS (YEARS)				
18-50	380 (31.2%)	215 (29.6%)	79 (36.9%)	36 (24.2%)
51-80	743 (61%)	455 (62.6%)	114 (53.3%)	98 (65.8%)
81-90	92 (7.6%)	56 (7.7%)	20 (9.3%)	14 (9.4%)
>90	3 (0.2%)	1 (0.1%)	1 (0.5%)	1 (0.7%)
Age 65 or younger	818 (67.2%)	494 (68%)	149 (69.6%)	81 (54.4%)
Age 65 or older	412 (33.8%)	238 (32.7%)	69 (32.2%)	69 (46.3%)
Age 75 or younger	1032 (84.7%)	618 (85%)	184 (86%)	114 (76.5%)
Age 75 or older	203 (16.7%)	121 (16.6%)	33 (15.4%)	36 (24.2%)
LITERACY				
Normal literacy ^a	1042 (85.6%)	636 (87.5%)	173 (80.8%)	123 (82.6%)
Low literacy ^b	162 (13.3%)	89 (12.2%)	35 (16.4%)	20 (13.4%)
Missing	14 (1.1%)	2 (0.3%)	6 (2.8%)	6 (4%)

Abbreviations: GED = general education diploma; SD = standard deviation

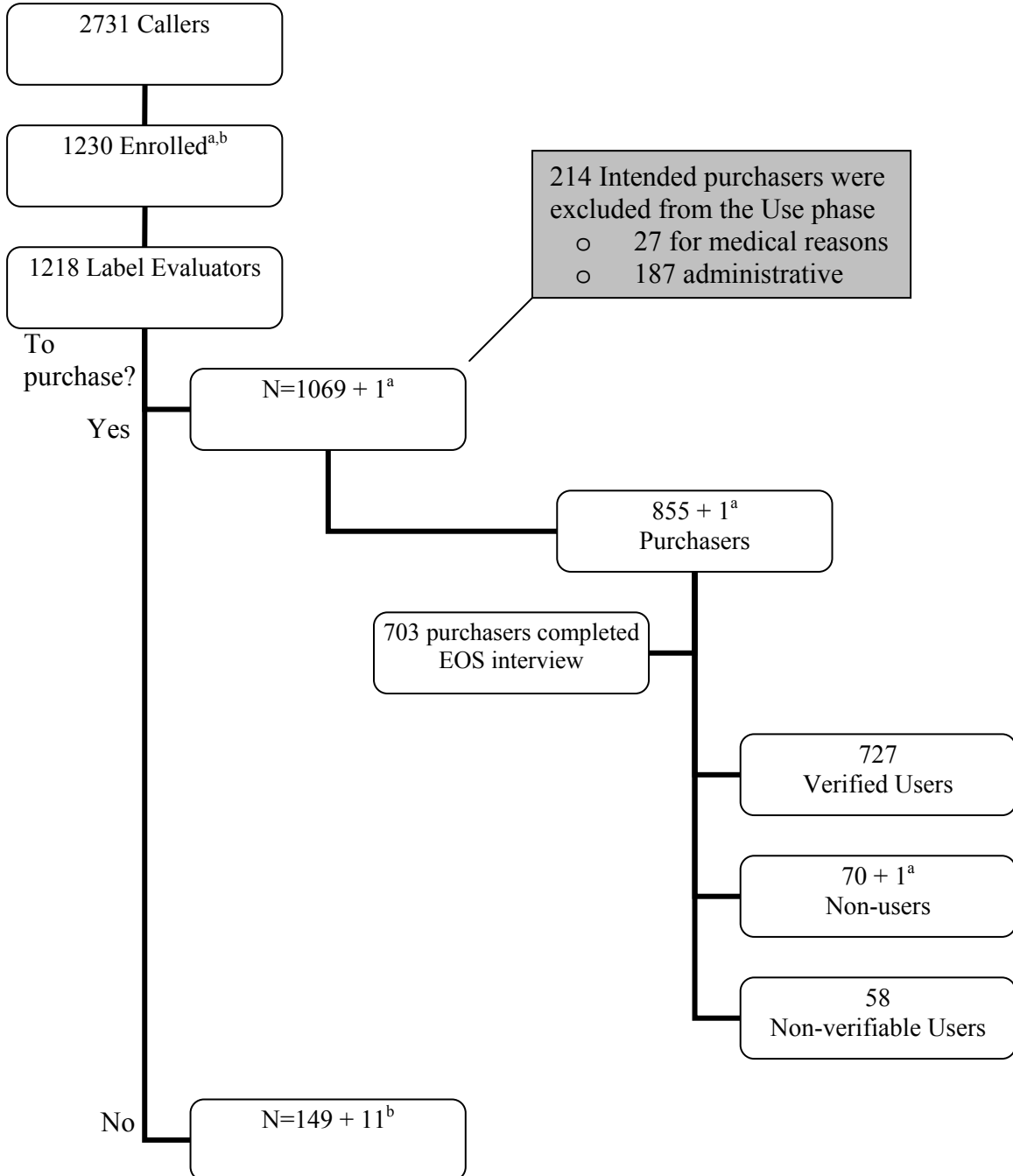
a Subjects scoring at least 61 on the REALM Test

b Subjects scoring less than 61 on the REALM Test

Source: Adapted from Sponsor's submission, Module 5.3.5.1, Section 10.4, Table 8, p. 57

Subject Disposition

There were 2731 potential subjects (“callers”) who responded to the recruitment ads. See **Figure 2**, **Table 2**, and **Table 3** for details on recruitment, enrollment, use and completion of the AUS.



a One protocol violator

b Eleven subjects did not provide enough enrollment data to allow them to evaluate the label or purchase the drug

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 9.7.1 Statistical Analysis Plan, p. 50.

Figure 2: Subject Disposition

Table 2: Screening Population – CONTROL Trial

Screening Population	N	% total
Began screening (callers)	2731	100%
Failed Inclusion or Met Exclusion Criteria ¹	561	20.5%
Male	45	8%
Pregnant or may be pregnant	5	0.9%
Employed by a pharmaceutical company	9	1.6%
Employed by a pharmacy	9	1.6%
Employed by an HMO or health insurance company as a healthcare professional	50	8.9%
Employed by a healthcare practice	81	14.4%
Ever trained or employed as a healthcare professional	363	64.7%
Participated in market research studies, product label studies or clinical trials (last 12 months)	108	19.3%
All fields missing	5	0.9%
Passed all screening questions	2170	79.5%
Appeared at pharmacy sites to begin enrollment	1230	45% of total screened

¹ Total value exceeds 100% because some subjects failed screening for more than one reason.
Source: Adapted from Sponsor's submission, Module 5.3.5.1, Section 10.1, Table 4, p. 52

No further questions were asked to learn why male or pregnant subjects (n=50; 8.9%) wanted to use the product. However, the number of these subjects responding to the recruitment flyers was low.

Table 3: Enrollment and Purchase Populations – CONTROL Trial (Purchase Decision = Yes)

Enrollment and Purchase Populations	N	% total
Completed enrollment interview ¹	1218	100%
Purchase Decision = Yes	1069	87.8%
Purchased medication (PD = yes)	855	80%
User (verified or non-verifiable)	785	
Non-user	70	
No drug dispensed (PD = yes)	214	20%
Administratively Excluded from Use phase (% not dispensed drug)	181	(84.6%)
Refused pregnancy test	12	
Did not sign Informed Consent	140	
Did not provide contact information	2	
Did not purchase drug	37	
Medical exclusion from Use phase ² (% not dispensed drug)	27	(12.6%)
Narrow-angle glaucoma	4	
Hematuria	13	
Pregnant	0	
Breastfeeding	5	
Known oxybutynin allergy	4	
Symptoms of UTI	3	
Other ³ (% not dispensed drug)	6	(2.8%)

¹ The total number of subjects who made an in-pharmacy purchase decision = 1230. Twelve subjects were excluded from completing enrollment. Nine did not answer any questions after saying “no” to purchase. Two subjects answered all questions except about race, but also said “no” to purchase. The final subject, 10-0033, purchased the product, but was a protocol violator and excluded from analysis. That subject admitted to being a nurse, an exclusion criterion, at the 3-week interview.

² Twelve subjects completed an “Excluded consent follow-up interview.”

³ These subjects did not sign the Informed Consent, refused the pregnancy test and did not have any additional data collected.

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 10.1, Table 5, p. 53

Table 4: Enrollment and Purchase Populations – CONTROL Trial (Purchase Decision = No)

Enrollment and Purchase Populations	N	% total
Completed enrollment interview ¹	1218	100%
Purchase Decision = No	160	13.1%
Did not answer eligibility questions	9	
No medical exclusion	147	
Had medical exclusion to prevent use	4	
Narrow-angle glaucoma	0	
Hematuria	2	
Pregnant	0	
Breastfeeding	0	
Known oxybutynin allergy	1	
Symptoms of UTI	1	

¹The total number of subjects who made an in-pharmacy purchase decision = 1230. Twelve subjects were excluded from completing enrollment. Nine did not answer any questions after saying “no” to purchase. Two subjects answered all questions except about race, but also said “no” to purchase. The final subject, 10-0033, purchased the product, but was a protocol violator and excluded from analysis. That subject admitted to being a nurse, an exclusion criterion, at the 3-week interview.

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 10.1, Table 5, p. 53

Refer to **Tables 3 and 4**. There were 727 verified users and 58 non-verifiable users (diaries were not completed). Twenty percent (20%, n=214) of subjects who met screening criteria and wished to purchase the product were excluded from entering the Use phase of the trial. Over 87% (n=187) of these patients were excluded for administrative reasons, i.e., refusing to sign consents, refusing pregnancy testing, ultimately deciding not to purchase the drug. Over 12% (n=27) had a medical reason for being excluded, and were referred to their physicians. Thirteen of these people reported hematuria not related to menses, or symptoms consistent with UTI (back pain and fever with hematuria, dysuria or cloudy urine). Of those, about 75% completed a follow up interview, and half saw a healthcare professional based on the recommendation from trial personnel. Diagnoses included UTI (n=2), pre-diabetes, Type 2 diabetes, recurrent kidney stones, and irregular menstrual bleeding. Others reported that hematuria was irregular, that they were already under a doctor’s care and were cleared to use the drug, or that they understood the risks, but they still wanted to try the product for their OAB symptoms. Subjects with narrow-angle glaucoma or who had a known allergy to oxybutynin stated that they chose to purchase the product hoping that the product would successfully treat OAB symptoms, that they did not notice the warnings, or that they misunderstood the label, i.e., believing that the usual anticholinergic side effects were signs of allergy to oxybutynin.

Of the 1069 who decided to purchase the drug, 230 (21.5%) made the decision correctly, i.e., according to proposed labeling. Thus, the other 839 (78.5%) had ineligibilities according to the label, but chose to purchase the drug and were allowed to do so. Label ineligibilities were contraindications or precautions proposed in the OTC label (see **Table 1** in Section 7). The ineligibilities spanned the gamut, from not having two or more OAB symptoms for at least three months, to not having spoken with a doctor about symptoms or diagnoses such as weight loss, excessive thirst, liver, or kidney disease. The

ineligibility most frequently reported by purchasers was the feeling of not being able to completely empty the bladder (n=323).

Analysis of Primary Endpoint

The primary endpoint was the proportion of subjects who did not stop use when they developed either new or worsening symptoms in accordance with the label directions. Interview questions addressed both urinary and non-urinary symptoms. New symptoms were those indicated anywhere on the label, but also included abdominal or pelvic pain.

The primary endpoint was the proportion that did not stop use derived from the population who used at least one patch (total user population). A subset proportion defined those with new or worsening symptoms who did not stop use from the population reporting new or worsening symptoms.

The threshold rate for misuse by the primary endpoint was set, *a priori*, at $\leq 5\%$.

The sponsor employed mitigation strategies to determine whether subjects who reported new or worsening symptoms, but continued using the product, had a clinically valid reason to do so. An interviewer asked questions about symptoms at the week 3, 7 and 12 interviews. The sponsor determined whether subjects who reported new or worsening symptoms continued use of the drug, based on diary entries. Dates of use were recorded in the subjects' Case Report Forms (CRFs). New symptoms were compared with symptoms listed in the label requiring subjects to stop use. Subjects who reported such symptoms and did not stop using the drug are defined as misusers for this endpoint.

Symptoms or diagnoses included:

- Urinary tract infection
- Bladder infection
- Flank (side) pain
- Lower back pain
- Fever or chills AND pain or burning while urinating
- Blood in urine unrelated to menses
- Cloudy urine
- Foul smelling urine
- Urinary retention
- Narrow-angle glaucoma
- Kidney stones
- Liver or kidney disease
- Unexplained weight loss
- Gastric retention
- Allergic reaction to patch
- Severe redness, itchiness, or blistering at the application site
- Began taking a diuretic
- Frequent urination with excessive thirst, extreme hunger, or increased tiredness
- Became pregnant
- Abdominal pain
- Pelvic pain

A panel of four physicians (three independent and one employed by the sponsor) reviewed the CRFs from these misusers. If the physicians reached consensus regarding acceptability of continued use in the face of such symptoms, the misuse was mitigated. Mitigation assessments were made in the context of risk of AEs. Minimal risk was required. If subjects demonstrated poor understanding of the label or another reason to stop use, their misuse was not mitigated. Factors considered to assess risk included:

- Postponement of use of the patch until symptoms resolved, followed by a restart

- Symptoms were mild and resolved quickly
- Subject visited a physician, or planned to do so, and was told to continue use
- Worsening was part of the normal variability of the condition
- Symptoms were unrelated to OAB or use of the drug
- Subject did not recognize that new symptoms were included on the label, but stopped once she did
- Symptoms had appeared before and were part of the condition

Table 5 shows how the total number of verified users responded after experiencing symptoms that should have indicated that they stop use. (Note the primary endpoint result in bold print.)

Reports of new, labeled symptoms, abdominal or pelvic pain, or worsening symptoms should have resulted in stopping use and seeking a medical opinion. The table shows a comparison of the sponsor’s assessment of misuse, a proportion of all verified users, and an assessment of a subgroup, a proportion of verified users who had pertinent symptoms indicating that they should stop use.

Table 5: Proportion of Subjects who did not Stop Use when they Developed New Symptoms or Worsening Symptoms – Verified Users

Primary Endpoint	Pre-mitigation n=727 (95% CI)	Post-mitigation n=727 (95% CI)
Total subjects who had no pertinent symptoms	586 (80.6%)	586 (80.6%)
Total subjects who had symptoms indicating stopping use	141 (19.4%)	141 (19.4%)
Total subjects who failed to stop use – sponsor’s proportion	14.4%(105/727) (12.0%, 17.2%)	3.4% (25/727) (2.2%, 5.0%)
Proportion of subgroup	74.5%(105/141) (66.4%, 81.4%)	17.7% (25/141) (11.8%, 25.1%)
Developed a new symptom	73	13
Developed worsening only	22	11
Developed new symptoms and worsening condition	10	1

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 11.1.1, Tables 13, 14 (p. 68, 69) and Tables 14-14-1 and 14-14-2.

The sponsor also assessed misuse of all 785 users of at least one patch. Above, only verified users are included, but the misuse rates did not significantly differ when all users are considered. The proportion of misuse of even a single patch was within the *a priori* threshold (3.4% < 5%). Another clinically relevant proportion is of misusers among subjects who reported symptoms that should have led them to stop use and seek a medical opinion (n=141). The pre- and post-mitigation misuse proportions from those users who failed to stop use are higher, and likely more relevant, than the misuse proportions derived from all users. Nearly 75% misused, pre-mitigation, whereas 17.7% misused, post-mitigation. While this proportion is higher than the pre-specified 5% threshold, the trial was not powered to evaluate this proportion. Misuse by subjects with

new or worsening symptoms should be evaluated in the context of the safety data collected from the trial, which is discussed in Section 7.

The sponsor assessed the primary endpoint by literacy, age (<65 years, 65-74 years, ≥ 65 , and ≥ 75 years), and race (whites versus non-whites). No notable differences were observed in the subgroups. Some subgroups had low sample sizes and, therefore, results may not be easily generalized to the population of likely users.

Table 6 compares the rates of misuse by race, age, and literacy subgroups for the primary endpoint. In the table, denominators in shaded areas reflect verified users of the identified subgroup. Denominators in unshaded areas reflect verified users who had new or worsening symptoms.

Table 6: Proportion of Subjects who Misused by Race, Age or Literacy for the Primary Endpoint¹

Primary (N=727)	Total Misusers – pre-mitigation		Total Misusers – post-mitigation	
Race	N	% total who had new or worse symptoms	N	% total who had new or worse symptoms
White (n=561)	79	75.5% (79/105)	15	14.3% (15/105)
Sponsor's proportion - White		14.1% (79/561)		2.7% (15/561)
Non-white (n=166)	26	72.2% (26/36)	10	27.7% (10/36)
Sponsor's proportion - Non-white		15.7% (26/166)		6% (10/166)
Age	N		N	
< 65 years (n=489)	57	68.7% (57/83)	14	16.9% (14/83)
Sponsor's proportion < 65		11.7% (57/489)		2.9% (14/489)
65-74 years (n=117)	23	82.1% (23/28)	5	17.9% (5/28)
Sponsor's proportion 65-74		19.7% (23/117)		4.3% (5/117)
≥ 65 years (n=238)	48	82.8% (48/58)	11	19% (11/58)
Sponsor's proportion ≥ 65		20.2% (48/238)		4.6% (11/238)
≥ 75 years (n=121)	25	83.3% (25/30)	6	20% (6/30)
Sponsor's proportion ≥ 75		20.7% (25/121)		5% (6/121)
Literacy²	N		N	
Literate (n=636)	96	76.2% (96/126)	24	19% (24/126)
Sponsor's proportion - Literate		15.1% (96/636)		3.8% (24/636)
Low literate (n=89)	9	60% (9/15)	1	6.7% (1/15)
Sponsor's proportion - Low literate		10.1% (9/89)		1.1% (1/89)

¹ Primary Endpoint is proportion that did not stop use if they developed a new, labeled symptom, reported abdominal or pelvic pain, or when their condition worsened.

² Two subjects did not provide responses to the REALM test.

Source: Adapted from Sponsor's submission, Module 5.3.5.1, Section 14.2, Tables 14-14-11 to 14-14-13, p. 248-256.

Proportions in the unshaded rows may be more clinically relevant, but the trial was not powered to determine significance of the misuse difference from the a priori threshold rate. The trial would have needed to be a great deal larger to capture enough subjects with new or worsening symptoms whereupon the misuse rate of the subgroup might offer a significant result. Of those subgroups in the unshaded rows, at best, 6.7%, and at worst, nearly 28%, did not stop use when the label clearly directed them to do so.

The FDA reviewer evaluated the sponsor’s rationale for mitigation of every subject who misused by the primary endpoint (n=91, total users included in sponsor’s datasets). For rationales that did not clearly meet one of the sponsor’s mitigation factors, he crosschecked the symptoms identifying misuse with AEs reported by the subjects. He agreed with the sponsor’s mitigation rationale in all instances except two. Removing two subjects from the post-mitigation rate did not affect the final result.

Table 7 shows that, overall, the majority of subjects reported improved OAB symptoms at any follow up interview. This table addresses users of at least one patch to show how subjects’ use decisions were affected by the state of their OAB symptoms at the time of their respective interviews. Of those who reported symptoms that stayed the same or worsened, the majority chose to continue using the drug. The most common reason to continue use was to see if the drug needed longer to work.

Table 7: Summary of Users' OAB Symptom Assessment and Action Taken

Subjects who reported OAB assessment ^a	Follow-up Week 3 (n=690)		Follow-up Week 7 (n=561)		Follow-up Week 12 (n=459)	
	Improved	483	70%	354	63.3%	272
Stayed the same ^b	187	27.1%	181	32.4%	171	37.3%
Continued use	137 (73.3%)		117 (64.6%)		146 (85.4%)	
Stopped use	50 (26.7%)		64 (35.4%)		25 (14.6%)	
Worsened ^b	20	2.9%	24	4.3%	15	3.3%
Continued use	12 (60%)		15 (63%)		11 (73%)	
Stopped use	8 (40%)		9 (37%)		4 (27%)	

^a These subjects responded to interview questions about the current state of their OAB symptoms compared to starting the drug (Week 3) or since the last interview (Weeks 7 and 12). Subjects reported stopping or continuing use based only on the status of their OAB symptoms.

^b The proportion of subjects who continued use or stopped use were determined based on all subjects (100%) whose symptoms either stayed the same or worsened.

Source: Adapted from Sponsor’s submission; Module 5.3.5.1, Section 11.1.4, p. 89, Table 21

Analysis of Mitigated Misuse - Secondary Endpoints

The proposed label instructs consumers to stop use and ask a doctor if their condition does not improve after two weeks. This direction is designed to avoid missing or avoid undue delay of a serious medical condition. The following secondary endpoints (SE) defined misuse in circumstances different from the primary endpoint. Important secondary endpoints included:

- SE3: proportion who did not stop use after two weeks of no improvement. This proportion includes the total number of such subjects divided by those who completed the week 3 interview and used patches for at least two weeks. (N=643)

Misuse by this endpoint was mitigated. Misuse was assessed by two employees of the sponsor. If not in agreement, a third reviewer (a physician employee) resolved the assessment. Subjects’ responses mitigating continued usage beyond two weeks were pre-specified. The sponsor mitigated use for several reasons:

- If subjects provided a thoughtful, informed reason to continue use

- If subjects talked to a physician after starting use and received advice to use beyond two weeks
- If subjects continued use beyond the week 3 interview, but stopped by the week 7 interview – captured users who may not yet have used the drug for two weeks
- If subjects had considered that the drug may need a longer duration of use to exert an effect. Symptoms at the week 7 interview must be “improved.”
- Subject stopped use between interviews.

The sponsor assessed the SE3 by literacy age (<65 years, 65-74 years, ≥ 65 , and ≥ 75 years), and race (whites versus non-whites). (See **Table 8**. Denominators in shaded areas reflect total users of a specific subgroup. Denominators in unshaded areas reflect users who had new or worsening symptoms.)

Some subgroups had low sample sizes, but the misuse rates were not starkly disparate across the groups. At the week 3 interviews, subjects were asked to compare the state of their symptoms, i.e., improved, the same or worse, from the time they began using the drug. Over 640 (n=643; 93.2% of those who completed the week 3 interview) subjects reported using the drug for at least two weeks.

Table 8: Proportion of Subjects who Misused by Race, Age and Literacy for SE3¹

SE3 (N=643)	Total Misusers – pre-mitigation		Total Misusers – post-mitigation	
Race	N	% total w/ no improvement	N	% total w/ no improvement
White (n=496)	122	80.8% (122/151)	60	39.7% (60/151)
Sponsor's proportion - White		24.6% (122/496)		12.1% (60/496)
Non-white (n=147)	23	63.8% (23/36)	11	30.5% (11/36)
Sponsor's proportion - Non-white		15.6% (23/147)		7.5% (11/147)
Age	N		N	
< 65 years (n=431)	85	75.2% (85/113)	42	37.2% (42/113)
Sponsor's proportion - < 65 years		19.7% (85/431)		9.7% (42/431)
65-74 years (n=104)	31	81.6% (31/38)	13	34.2% (13/38)
Sponsor's proportion - 65-74 years		29.8% (31/104)		12.5% (13/104)
≥ 65 years (n=212)	60	81.1% (60/74)	29	39.2% (29/74)
Sponsor's proportion - ≥ 65 years		28.3% (60/212)		13.7% (29/212)
≥ 75 years (n=108)	29	80.5% (29/36)	16	44.4% (16/36)
Sponsor's proportion - ≥ 75 years		26.9% (29/108)		1.8% (16/108)
Literacy²	N		N	
Literate (n=571)	129	77.2% (129/167)	65	38.9% (65/167)
Sponsor's proportion - Literate		22.6% (129/571)		11.4% (65/571)
Low literate (n=70)	16	80% (16/20)	6	30% (6/20)
Sponsor's proportion - Low literate		22.9% (16/70)		8.6% (6/70)

¹ A subject had no improvement if they responded to Question 2 in the 3-week interview saying symptoms were the same or worsened, and they had two weeks of verified use. No similar questions were asked in later interviews.

² Two subjects did not provide responses to the REALM test.

Source: Adapted from Sponsor's submission, Module 5.3.5.1, Section 14.2, Tables 14-14-23 to 14-14-25, p. 301-309.

The sponsor determined proportions of subjects without improvement who did not stop use, based on the total number of subjects who took the drug for two weeks. Combining the total users and misusers for “white” and “non-white” subjects in the fully shaded rows in **Table 8**, the total misuse rates are 22.6% and 11%, pre- and post-mitigation, respectively. Another misuse proportion is based on just the number of subjects who took the drug for two weeks with no improvement (no change or worsening). Here, combining “white” and “non-white” in the unshaded rows, the results are 77.5% and 38%, pre- and post-mitigation, respectively.

Shown in the unshaded rows of **Table 8**, none of the post-mitigation proportions of misusers, from any subgroups (race, age or literacy), are lower than 30%. From review of the sponsor’s line listing of misuse by SE3, it also appears that many subjects (> 50%) were mitigated based on responses from the week 7 interviews. Subjects who reported no improvement at week 3, but who had improvement at week 7, were mitigated if they offered a “thoughtful, informed reason,” as per the pre-specified mitigation criteria, to continue use. Several of these subjects had received advice from their physicians to continue using the drug. Further review of the number of subjects (n=169) who only reported no change to their OAB symptoms at the week 3 interview showed that, by the week 12 interview, 54% continued to use the drug (most had still not spoken with their doctors).

Further, the sponsor assessed, by review of diary entries, the median time to discontinue use by subjects who had no improvement after two weeks of use. For subjects who reported worsening OAB symptoms at the week 3 interview, the median number of days to discontinue use, following initial worsening, was 8.5 days. For subjects who reported no change in symptoms at the week 3 interview, the median was 36 days. Thus, results show that many subjects who had no effect from the Oxytrol TDS continued to use the product even when the label clearly instructed stopping use and seeing a physician beyond two weeks without an effect.

- SE5: the proportion of subjects who misuse based on incorrect duration (> 4 days) and/or simultaneous use. This proportion was determined by all subjects who used at least one patch. The sponsor used diary entries to assess misuse. Subjects with diaries that were missing starting or ending dates were excluded.
 - At the EOS interview, subjects were asked how many days they were allowed to wear a single patch, and how many patches they were allowed to wear at the same time. Subjects who used patches for longer than 4 days had to meet all of the following criteria for their misuse to be mitigated:
 - No patch was used for ≥ 8 days
 - Two or fewer patches were used for 6-7 days
 - Total number of patches misused $\leq 25\%$ of total patches used
 - Subject gave a valid reason for misuse, e.g., “I forgot to remove.”
 - Mitigation of simultaneous use was allowed if
 - A subject’s diary contained an obvious entry error

- Entries were repeated at the end of one diary and the beginning of the next
- Subjects denied misuse, or
- Subjects were told by their physician that such use was acceptable

Subjects who wear a patch for longer than directed may be at higher risk for application site reactions. However, such reactions are usually self-limited and consumers may simply remove the patch if their skin becomes irritated. The proposed label includes a skin irritation warning. However, use of multiple patches may have greater risk for adverse drug reactions, including anticholinergic-related events, particularly CNS-related events, and overdose. Such use could be particularly dangerous for elderly consumers who are most likely to use the drug.

Pre-mitigation for SE5, of the total number of verified users of at least one patch (n=727), 370 (50.9%; 95% CI: 47.9%, 55.4%) misused based on prolonged duration or simultaneous use (**Table 9**). Thirty-four subjects (4.7%) misused by a combination of both prolonged and simultaneous use. Twenty-seven subjects who misused by simultaneous use only (27/77; 35.1%) were over age 65. Misuse was mitigated for all of them but seven. Additionally, the sponsor notes that individual patches were applied correctly, as per diary entries, 84.9% and 95.9% of the time for those subjects who misused by prolonged duration and simultaneous use, respectively. The vast majority of subjects had few and sporadic misuses of patches over their total duration and quantity of use.

Table 9: Proportion of Subjects who Misused the Patch by Prolonged Duration or Simultaneous Use (SE5)

Secondary Endpoint 5	Total Subjects pre-mitigation (n=727); N (%; 95% CI)	Total Subjects post-mitigation (n=727); N (%; 95% CI)^a
Incorrect Use (Total)	370 (50.9%; 47.9%, 55.4%) ^b	152 (20.9%; 18.3%, 24.4%)
Misuse by each method separately		
Incorrect Use (> 4 days use)	333 (45.8%; 42.8%, 50.2%)	155 (21.3%; 18.7%, 24.8%)
Incorrect Use (simultaneous use)	77 (10.6%; 8.6%, 13.3%)	22 (3.0%; 1.9%, 4.6%)

^aThe number of misusing subjects, post-mitigation, result from the separate methods of incorrect use, not the total post-mitigation number.

^bData from the sponsor's submission is slightly incorrect. Its stated total proportion of incorrect use, 51.7%, is actually 50.9% (370/727). Similar minor discrepancies apply to all misuse rates in this table.

Source: Adapted from sponsor's submission, Module 5.3.5.1, Section 11.1.7, Tables 40, 41 and 43.

Table 10 compares the rates of misuse by race, age, and literacy for SE5. Rates of misuse increase with age (18.3% to 28.6% post-mitigation). The table also shows rates by simultaneous use only (sim. use only). There were few subjects misusing by this method. The proportions did not appear to differ greatly by subgroup. While misuse rates for subjects 65-74 years of age and low literate subjects were highest, these categories included the lowest total numbers of misusing subjects.

Table 10: Proportion of Subjects who Misused by Race, Age and Literacy for SE5

SE5 (N=727)	Total Misusers – pre-mitigation			Total Misusers – post-mitigation			
	Race	N	% total (95% CI)	Sim. Use only (%)	N	% total (95% CI)	Sim. Use only (%)
White (n=553)	301	54.4%	(50.2%,58.6%)	60 (10.8%)	129	23.3%	(19.9%,27.1%)
Non-white (n=163)	69	42.3%	(34.6%,50.3%)	17 (10.4%)	23	14.1%	(9.2%, 20.4%)
Age							
< 65 years (n=481)	226	47%	(42.5%,51.6%)	50 (10.4%)	88	18.3%	(14.9%, 22%)
65-74 years (n=116)	68	58.6%	(49.1%,67.7%)	15 (12.9%)	30	25.9%	(18.2%,34.8%)
≥ 65 years (n=235)	144	61.3%	(54.7%,67.5%)	27 (11.5%)	64	27.2%	(21.6%,33.4%)
≥ 75 years (n=119)	76	63.9%	(54.6%,72.5%)	12 (10.1%)	34	28.6%	(20.7%,37.6%)
Literacy							
Literate (n=629)	325	51.7%	(47.7%,55.6%)	65 (10.3%)	133	21.1%	(18%, 24.5%)
Low literate (n=86)	44	51.2%	(40.1%,62.1%)	12 (14.0%)	18	20.9%	(12.9%, 31%)

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 11.1.8, Tables 14-14-35-1 to -3, p. 391

Overall, 21% of verified users misused. Frequently reported reasons for prolonged use included “forgot to remove the patch” (n=165; 50% of those who provided a reason at the EOS interview), denial of prolonged use (n=93; 28.2%), and misunderstood label directions (n=38; 11.5%). For simultaneous use, most subjects denied misuse (n=59; 85.5% of those reporting reasons), or reported only replacing a patch (n=7; 10.1%). Three reported forgetting to remove the prior patch. All of these reasons allowed for mitigation of misuse.

Other reasons for misuse by either method do not allow for mitigation (n=82/330 who reported a reason; 24.8%), including misunderstanding the label (n=39; 9.8%), inconvenience (n=19; 5.8%), help with symptoms (n=3; 4.3%), and other, unidentified reasons (n=21; 5.3%). The large majority of unmitigated misuse was for prolonged use, and subjects may have reported more than one reason for misuse. These reported reasons may indicate a lack of understanding of the proposed label directions, or of the severity of warnings and precautions on the label. Of all misusers who reported their reasons for misuse, over half reported forgetting to remove a patch prior to placing a new one. This was 21.4% of all users (168/785).

Of note, at the EOS interview, many subjects were not asked about their questionable or discrepant diary entries to confirm recording errors. All subjects replied “one” when asked about the number of patches allowed to be applied at one time. While the large majority responded with reasons allowing for mitigation, four responded that they used

multiple patches simultaneously because they thought it would help with symptoms, or misunderstood the label.

7. Summary of Safety Profile

Section 7 summarizes the safety data from the

- CONTROL Trial (the actual use study reviewed in section 6, above)
- MATRIX Study (a postmarketing safety study following prescription Oxytrol users)
- Postmarketing databases, including FDA's Adverse Event Reporting System (AERS), the World Health Organization (WHO) database, and the American Association of Poison Control Center (AAPCC) database

The section ends with a summary of safety topics pertinent to oxybutynin TDS.

SAFETY SUMMARY – CONTROL TRIAL

The CONTROL trial evaluated use of oxybutynin transdermal system by 785 subjects (727 verified users and 58 non-verifiable users) in a simulated OTC environment. Subjects' label evaluations, purchase decision-making and home use are to assess if subjects use the patch safely and properly, and to assess the adverse events reported during use. The Use phase of the trial was 84 days (12 weeks). Based on diary entry data from verified users (n=727), median exposure to the drug over the duration of the trial was 45 days. The mean exposure to the drug was 44.6 ± 23 days.

The sponsor describes label ineligibilities as those symptoms or conditions, included in the proposed OTC label (Refer to Appendix 2), that consumers may have, but that indicate they should not use the product or that they should seek medical advice. The symptoms or conditions include not meeting the OAB symptom conditions, possible UTI (fever or chills with dysuria, or hematuria, or back or flank pain, or cloudy, foul-smelling urine), stress incontinence only, diagnosis of urinary or gastric retention, narrow-angle glaucoma, or allergy to oxybutynin. Narrow-angle glaucoma and drug allergy were exclusion criteria in the AUS. The label cautions consumers to speak with their doctor if they have risk factors for diabetes (a history of diabetes in the immediate family, excessive thirst, extreme hunger, or increased tiredness), unexplained weight loss (conservative indicator of bladder cancer risk when reported with dysuria, hematuria, or flank/back pain), liver or kidney disease (including kidney stones), or are using diuretics or other prescription drugs indicated for treatment of OAB.

Table 1 shows the purchase and use decisions of subjects reporting these label ineligibilities. More details of important safety issues are included in the issue-specific sections below.

Table 1: Purchase and Use Decisions by Subjects with Label Ineligibilities^a

	Total Evaluators of Label N=1218(%)^b	Purchase Decision=Yes N=1069	Dispensed Drug N=855	Used Drug N=785(%)	Spoke with Doctor & Used N=181^c
Potential Safety Issue					
< 2 OAB symptoms or < 3 months duration	179 (14.7)	138	103	88 (11.2)	11
Stress incontinence	315 (25.9)	281	214	198 (16.3)	^c
Possible UTI	260 (21.3)	229	166	154 (19.6)	19
Diabetes risk	516 (42.4)	454	351	321 (40.9)	79
Bladder cancer risk	188 (15.4)	163	107	100 (12.7)	12
Diuretic use	152 (12.5)	131	104	98 (12.5)	47
Liver/kidney disease	99 (8.1)	81	67	59 (7.5)	17
Incomplete emptying	522 (42.9)	458	357	323 (41.1)	3
Gastric retention, allergy, and/or narrow angle glaucoma ^d	36 (2.9)	35	21	20 (2.5)	0
Other OAB drug use	176 (14.4)	146	118	110 (14)	14

a Some subjects may be counted more than once if they reported symptoms that met more than one criteria.

b The total number of label evaluators following enrollment.

c This data was not reported for all subjects who reported stress incontinence.

d The label evaluators may have reported more than one condition. All subjects reporting narrow angle glaucoma (n=4) or allergy (n=5) were excluded from the Use phase of the trial. All four subjects reporting narrow angle glaucoma and four of five subjects with allergy wished to purchase the drug.

e This is the total number of subjects who spoke with their doctor after purchase around the time of their initial use.

Source: Adapted from Sponsor's submission; Module 5.3.5.1, several Tables within Sections 11.1 and 11.2.

Of all subjects who completed enrollment procedures and evaluated the label (n= 1218), 931 (87.1%; 931/1069) who made a decision to purchase the drug, met the condition of having two or more OAB symptoms for at least three months. Two hundred fourteen who said they wanted to purchase the drug were excluded for various reasons. (Refer to **Table 3** on page 39.) Eight hundred fifty-five people received study drug. Of these, only 752 who had two symptoms for three months were dispensed study drug because 179 were excluded from the Use phase for other medical or administrative reasons. One hundred three who did not have two symptoms for three months also received study drug because they did not meet other criteria for excluding. Nearly 89% (697/785) of subjects who used the drug met the symptom conditions considered positive for OAB. Twenty-two of those who did not meet the conditions reported having been told by their physicians that they had OAB. Eleven of the 22 used the drug.

There were 172 subjects (54.6%, 172/315) who reported having stress incontinence, but otherwise met the labeled symptom conditions for OAB in that they reported urgency and frequency. Most of these subjects chose to purchase the drug (89.5%, 154/172) and many used it (72.7%, 112/154). Among the subjects who completed the follow-up interviews, 74.5%, 63.4% and 59.7% of users initially reporting stress incontinence, reported improvement of their OAB symptoms at the 3, 7, or 12 week follow-up interview, respectively. Thirty-one (27.7%; 31/112)

spoke with their doctor around the start of use, and, based on End-of-study (EOS) interviews, over 60% were cleared to continue using the drug.

Nearly 70% of subjects who reported possible UTI-related symptoms at the week 3 interviews indicated that their OAB symptoms had improved. The possibilities of UTI, diabetes, or bladder cancer mimicking OAB are further addressed below in the section **Primary Safety Concerns**.

The most frequently reported ineligibility was not being able to completely empty the bladder. Subjects were not specifically asked if they had “urinary retention.” The sponsor believes that many consumers with OAB may feel that they cannot empty their bladders in efforts to explain their urinary urgency and frequency. Importantly, nearly 65% of these subjects reported improvement of their OAB symptoms at any of the follow up interviews. **Table 1** shows that only three subjects with incomplete emptying spoke with their doctors before use, thus supporting subjects’ possible interpretations of their symptoms.

Over 87% (86/98) of subjects who reported using a diuretic at enrollment continued to use one as reported at the EOS interviews. Most subjects who were previously taking a prescription drug for OAB symptoms chose to stop use (75.4%, 83/110) once they entered the Use phase of the trial. Most subjects with label ineligibilities who spoke with their doctor, decided to use the product.

Common Adverse Events

In total, 519 subjects (66.1% of total users) reported at least one AE. Subjects reported 975 AEs total. Almost 37% (n=359) were considered possibly or probably drug-related by the sponsor’s assessment. Over 75% of all AEs were mild in severity. **Table 2** shows the number and percentages of the most pertinent and commonly reported AEs stratified by the subjects’ age. There did not appear to be any significant difference in overall AE reporting, or SAE reporting, stratified by age (< 65 years; > 65 years; > 75 years). From among subjects in each age group, 65%, 68.3% and 67% reported at least one AE, respectively. Subjects reporting SAEs made up 4%, 5.4% and 5.5% of all those in each respective age group. Of note, women < 65 reported application site irritation and constipation with greater frequency, while older subjects reported UTI, cystitis and dysuria in greater proportion.

Table 2: Frequently Reported AEs by Age

	All Users (N1=785)		Users Age < 65 years (N2=529)			Users Age 65-74 years (N3=129)			Users Age > 75 years (N4=127)		
	N	%N1	N	%N1	%N2	N	%N1	%N3	N	%N1	%N4
With ≥ 1 AE	519	66.1%	344	43.8%	65%	90	11.5%	69.8%	85	10.8%	67%
With SAE	35	4.5%	21	2.7%	4%	7	0.9%	5.4%	7	0.9%	5.5%
Application site irritation	142	18.1%	112		21.2%	19		14.7%	11		8.7%
Urinary tract infection	50	6.4%	27		5.1%	9		7%	14		11%
Dry mouth	32	4.1%	23		4.3%	4		3.1%	5		3.9%
Urge incontinence	24	3.1%	14		2.6%	5		3.9%	5		3.9%
Constipation	20	2.5%	17		3.2%	2		1.6%	1		0.8%
Back pain	18	2.3%	10		1.9%	5		3.9%	3		2.4%
Cystitis	16	2%	7		1.3%	5		3.9%	4		3.1%
Dysuria	12	1.5%	4		0.8%	3		2.3%	5		3.9%

Source: Adapted from Applicant's submission; Module 5.3.5.1, Section 12.4.5, Table 78, p. 173

These reported AEs are frequently associated with anticholinergic drugs (dry mouth, constipation), transdermal drug formulations (application site reactions) and older age female subjects (UTI, urge incontinence, cystitis). See the **Primary Safety Concerns** below.

Nonfatal Serious Adverse Events

Forty-one subjects reported 48 SAEs over the duration of the trial. Only 35 subjects were users. Only one SAE was considered possibly related to the study drug. This subject (ID# 35-0037) had unrelated surgery on a rotator cuff. She did not completely recover from anesthesia exposure in the post-operative period, and she had been wearing a patch at that time. A drug interaction was considered possible. SAEs included three UTIs, three strokes, four cases of back or chest pain, and two diagnoses of cholecystitis as the only reports made more than twice.

Deaths and Discontinuations

Of the entire safety population (n=785), there was one unrelated death. A user with HIV died of complications from viral pneumonia. There were 152 (19.4%) subjects who permanently discontinued the test drug for any reason; 141 (18%) discontinued due to any adverse event (AE). The most common primary reasons subjects gave for stopping use of the drug were “side effects” (n=127), “not effective” (n=96) and “non-medical personal reasons” (n=45). Seventeen reported that their reason was because their doctor instructed them to stop use.

Among subjects who discontinued due to AEs, 13 reported SAEs. Overall, 27.2% of all those who reported at least one AE (141/519) discontinued use of the drug. Of these, 110 subjects reported AEs possibly or probably related to the drug. Thirty-one subjects (28.2%), reporting an AE at least possibly related to use of the test drug, were > 65 years of age. Most of the 141 who discontinued use of the test drug continued to participate in follow up interviews for the duration of the trial.

The most frequently reported AEs by subjects who discontinued use of the test drug included “General disorders and administration site conditions” (n=73), followed by “Gastrointestinal disorders,” “Nervous system disorders,” and “Infections & infestations” (n=16 each). Pertinent AEs included “application site irritation” (n=54), “dry mouth” (n=6), “UTI” or “cystitis” (n=13), “dizziness” (n=6), and “urge incontinence” (n=8). Subjects who discontinued due to SAEs most frequently reported UTI (n=3), fractures (n=2), or stroke (n=2). See below for further details.

Primary Safety Concerns

Urinary Tract Infection (UTI)

Nearly 20% (154/785) of all users reported at least one labeled contraindication that could be consistent with UTI:

- pain or burning when urinating
- fever or chills in conjunction with pain or burning when urinating
- hematuria

- cloudy or foul-smelling urine
- lower back or side pain

Most of these subjects (**Table 3**) were still allowed to enter the Use phase, as only three met the stricter exclusion criteria of back pain with or without fever and either dysuria, hematuria or cloudy urine. As above, thirteen were excluded from the Use phase for reporting isolated hematuria unrelated to menses.

Table 3: Actions of Subjects with Possible UTI Symptoms Following Purchase Decision – Enrollment Interview

Purchase decision (PD) by subjects with possible UTI symptoms	N (% total)	Subjects not dispensed drug ^a	Used patch?		Talked to Doctor before use	
			Yes ^b	No	User	Non-user
PD = yes	229 (88.1%)	63	154	12	19	0
PD = no	31 (11.9%)	31	NA	NA	NA	NA
Total	260	94				

^aSubjects who said “yes” to purchase were excluded from Use phase for a medical exclusion or administrative reason, i.e., did not sign Informed Consent

^bTotal users

Source: Adapted from Sponsor’s submission, Module 5.3.5.1, Section 11.2.3.2, Table 60, p. 151

Of the subjects who reported possible UTI symptoms and used the patch (n=154), only eight (5.2%) were diagnosed with UTIs over the course of the trial. Seven of these subjects recognized the symptoms or were diagnosed through routine care; i.e., urinalysis at an office visit. The eighth subject was diagnosed based on her end-of-study (EOS) urinalysis result. Another 26 users developed new UTI-like symptoms over the duration of the trial. Nearly 58% stopped using the patch once the new symptoms appeared. Four were subsequently diagnosed with UTI. Nine continued using the patch without having spoken to their doctors. This misuse was mitigated for seven of these subjects and the mitigations seemed appropriate.

The sponsor decided to label the product for consumers with persistent OAB symptoms, duration beyond three months, partly to limit the risk that symptoms of acute UTI would mimic idiopathic OAB. As shown in Table 1, the large majority of subjects reported having two or more OAB symptoms for at least three months. Based on review of the enrollment interviews, very few subjects (2.7%, 33/1218 label evaluators) reported having symptoms for equal to or less than one month, further limiting the likelihood that symptoms were indicative of acute UTI. Five users who did not meet the symptom conditions for OAB were diagnosed with UTI or bladder infection over the course of the trial; however, four diagnoses came at least three weeks after their first patch application. The fifth subject (ID#11-0085) reported burning on urination on her first day of patch application. She had reported having two OAB-like symptoms for two months, and did not report symptoms consistent with UTI during enrollment. Five days after dysuria began, she sought medical evaluation and was diagnosed and treated for a UTI and yeast infection. She had applied only one patch, and did not continue using the drug. All five subjects with UTI recognized their symptoms and spoke with their healthcare providers when the symptoms began. Two continued using the drug.

In total, 61 subjects (7.8% of all users) reported UTIs or bladder infections, sometimes multiple infections, over the duration of the trial. Five of these infections were diagnosed in subjects reporting any SAEs. These were not the same five people described earlier. Three UTIs were considered serious themselves; the other two were identified in unrelated serious reports. Two of these subjects with SAEs discontinued use of the drug at the time of their diagnoses. The third subject was hospitalized for intravenous antibiotic treatment four days after having stopped use of the drug due to skin irritation. The fourth and fifth subjects initially continued use after UTI treatment; one following surgery for pelvic floor prolapse, and the other after completing treatment for pelvic inflammatory disease and a UTI. This last subject then permanently discontinued use of the drug after sustaining multiple fractures in a motorcycle accident. All five subjects reporting UTIs in serious cases reported having OAB symptoms ranging in duration from 8 months to 20 years. Only one (ID# 31-0006) of the five had a UTI-like symptom upon enrollment.

Finally, 461 subjects (453 users and eight non-users) returned for the EOS urinalysis at their pharmacy sites. Nearly 49% (225/461) had at least one positive finding, where blood, protein, glucose, nitrite, or leukocytes were tested. Two hundred twenty (220) completed the Use Phase Follow Up Interviews for these positive urinalyses. Another 69 subjects also completed this interview, 68 reporting seeing their doctor for a labeled precaution or condition, and one having been previously withdrawn from the study due to a possible UTI. Of the 220 subjects with positive urinalyses, 143 (65%; 143/220) reported seeing their healthcare provider after receiving the results. It appears on review that approximately 55 UTIs or bladder infections were diagnosed or treated. Many subjects appeared not to report any symptoms, as several of the diagnoses were made on the results of the urinalyses alone. However, others who reported symptoms and had positive urinalyses did not appear to receive any treatment.

While some subjects who chose to purchase and use the drug had at least one symptom that could indicate a UTI, the majority of subjects reported having OAB symptoms for more than one month. Symptoms of acute UTI would not likely be tolerated by most persons for that length of time, and it appears that the few subjects who had shorter term OAB symptoms and UTI were able to easily recognize the symptoms and seek medical evaluation. Most of these subjects were diagnosed after several weeks of patch use. Of the 61 total subjects with UTI or bladder infection, only eight had reported possible UTI symptoms at the enrollment interview. Seven of the eight appeared to have and recognize UTI symptoms and seek evaluation. The eighth subject appeared to be asymptomatic at diagnosis.

UTIs are fairly common in the older female population most likely to use this product. Review of the subjects' medical summaries supports how difficult it can be to diagnose UTI. Most consumers in the CONTROL trial did not confuse UTI and idiopathic OAB; it does not appear that there were significant delays in diagnosis of UTI. No one became septic during the study.

Urinary Retention

A large majority of subjects who chose to purchase the drug had label ineligibilities of lesser significance than absolute contraindications. The most frequently reported ineligibility was the feeling of not being able to completely empty the bladder. Subjects were not specifically asked whether they had been diagnosed with “urinary retention,” because the sponsor felt this was not consumer-friendly language. Of 522 users (66.5%; 522/785) who reported this feeling, only three spoke with their doctors prior to use.

Six subjects reported instances of new or worsening urinary retention over the duration of the trial. All were considered possibly related to use of the test drug. One of these subjects (ID# 37-0142) had a history of incomplete bladder emptying prior to use. This subject reported that her doctor cleared her to continue use, and was aware of her worsening symptoms. Another subject (ID# 24-0006) reported retention within a few days of use. She discontinued use of the drug on the advice of her doctor. None of the events were serious; all events were rated by the investigators as mild, resolved on their own, and only subject 24-0006 permanently discontinued use of the drug or the trial.

Diabetes

During enrollment, 516 subjects reported either a family history of diabetes or possible diabetes symptoms. Nearly 41% (n=321) purchased and used the drug. Additionally, 125 label evaluators had a prior diabetes diagnosis, and 79 of them (63.2%) were verified users of the drug. At the 3 week and 7 week interviews, at least 63.5% of those users with diabetes risk who completed the interviews reported improved OAB symptoms.

Two cases of diabetes were reported by users during the trial. One 41-year-old subject (ID #12-0121) was diagnosed with Diabetes Mellitus Type 1 two weeks after starting the drug and, on the advice of her doctor, discontinued use of the drug at that time. She reported having OAB symptoms for five years. She also reported having frequent urination with excessive thirst, hunger and tiredness, denying any family history of diabetes. She had initially seen her doctor with a complaint of foot pain, later considered neuropathic pain due to her diabetes. She briefly restarted use after her diabetes diagnosis, but stopped due to the cost of the product. The other subject had an ongoing diabetes diagnosis that worsened prior to beginning use. Two other cases of elevated blood glucose were reported. Both either resolved or improved.

There was one subject diagnosed with Diabetes Mellitus Type 2 after being excluded from the Use phase of the trial. She was excluded due to hematuria unrelated to her menses. This 53-year-old subject (ID# 15-0050) was diagnosed with both Type 2 diabetes and UTI. She had reported at least one year of urinary frequency and urgency, with four months of urge incontinence. She had a family history of diabetes and reported excessive thirst, hunger and tiredness. She saw her doctor after exclusion from the trial, as per the protocol’s referral procedures, where the diagnoses were made. This subject reported having been previously told by her doctor that she had OAB.

In total, two users (0.2%; 2/785) were diagnosed with diabetes during the trial. Both subjects reported longstanding OAB symptoms (one year and five years). After review

of their CRFs, there is no information that indicates that their diagnoses of diabetes were delayed due to misrecognition of their symptoms. In fact, subject 12-0121 reported improvement at the 3-week interview. Additionally, both subjects sought initial medical evaluation for seemingly unrelated symptoms (foot pain and hematuria).

Bladder Cancer

Proposed warnings on labeling that could be consistent with a diagnosis of bladder cancer include unexplained weight loss with pain and burning with urination, hematuria, or flank or back pain. In the CONTROL trial, 163 of 188 with reported symptoms chose to purchase the drug. One hundred (100) subjects used the drug. Only 12 spoke with their doctors before use. No cases of bladder cancer were diagnosed during the trial.

Gastric Retention and Narrow Angle Glaucoma

There were 27 subjects who reported gastric retention. Twenty chose to purchase the product and used it. None spoke with their doctors, and they were not asked why not. Seven were either excluded for medical or administrative reasons, or chose not to use the drug after purchase. All four subjects reporting narrow angle glaucoma wished to purchase the product, but were excluded from the Use phase of the trial. There were no reports of worsening gastric retention or any form of glaucoma.

Allergic Reactions

True allergic reactions are difficult to determine. Several Preferred Terms (PTs) could possibly indicate allergy, and there were many that made up the “Allergic Reaction” AE sub-population established by the sponsor. Hypersensitivity was reported eight times. There was one SAE reported where a subject had a reaction to a muscle relaxant, tizanidine, while also using the patch. Overall, 185 subjects reported an AE included in this sub-population. Seventy eight subjects discontinued use due to an AE. Most of them were skin related. From review of a sample of these reports, there did not appear to be any true allergic reactions.

Skin Reactions

There were 186 skin reactions (19.1% of all AEs) reported by 177 users (22.5%, 177/785). One report of skin blistering was serious, but this subject (ID# 26-0063) had completed the Use phase of the trial nearly three months prior to the time of the incident, and the blisters had appeared two days prior to hospitalization. She required wound care and unidentified intravenous treatment. The most frequently reported PT was “application site irritation” (n=142) followed by “application site reaction” (n=12) and “application site erythema” (n=9). Most reports are probably related to the patch. The large majority (177/186) were mild in severity and resolved. However, seventy-three subjects discontinued the study drug permanently due to skin AEs. No skin reactions worsened after patch removal. Risks of skin irritation can be adequately labeled, and simply addressed by removing the patch from the skin and using an oral formulation of drug.

Anticholinergic effects

A total of 105 related AEs (10.8% of all AEs) were reported by 89 users. PTs included dry eye, vision blurred or other affects to vision, constipation, dry mouth, balance disorder, dizziness, somnolence, dry throat or dysphonia. The most frequently reported PTs were “dry mouth” (n=32), “constipation” (n=20), and “dizziness/somnolence” (n=29). Over 90% were mild in severity, and none were serious. Most (87.6%) were assessed by the investigators as possibly or probably related to use of the patch. Twenty-five subjects permanently stopped use of the drug. Most (90%) were resolved or improved upon follow up interviewing, and none had worsened.

Disorientation and Confusion

A total of 79 pertinent AEs were reported by 78 subjects. There was likely some overlap in the specific AEs and number of reporting subjects since there was overlap in the PTs used to make up the AE sub-populations, “disorientation,” “confusion” and “anticholinergic effects.” The most frequently reported PTs were “dizziness/somnolence” (n=29), and “depression” (n=5). Two AEs were serious (schizoaffective disorder and convulsive syncope), but unlikely related to use of the study drug. Both subjects had histories of similar conditions prior to enrollment. Only one subject (difficulty chewing) permanently discontinued use of the study drug.

Falls and Accidents

In total, there were 17 subjects with 19 related AEs. Three subjects permanently discontinued the study drug. Seven were serious reports describing falls or accidents identified in the provided list of narratives. Only three of those subjects were using the drug at the time of their incidents:

- 57-year-old subject with history of multiple sclerosis and foot drop fell and sustained a cut to her head while using the patch. She believed the fall was due to her foot drop. The fall was considered unlikely related to use of the drug.
- 58-year-old subject without significant medical history sustained multiple fractures after a mini-bike accident. She had been using the patch at the time of the accident.
- 57-year-old subject with history of prior back surgery tripped and fell sustaining multiple fractures. She had been using the patch at the time.

SAFETY SUMMARY – POSTMARKETING EXPERIENCE

Oxytrol® has been marketed in the U.S. since June 2003. It has also been marketed worldwide in several countries for several years. The sponsor describes total global sales from initial marketing until February 2011 as 40 million patches distributed. In the U.S. alone, over 27 million patches have been sold over the same time period.

Twenty- six periodic safety reports have been submitted to the FDA since marketing began.

MATRIX Postmarketing Safety Trial

The sponsor provided safety data from the **MATRIX** trial (**M**ulticenter **A**ssessment of **T**ransdermal Therapy in Overactive Bladder with Oxybutynin TDS; Protocol OXY0402)

conducted by the NDA holder. Subjects in this trial had OAB symptoms, determined by a physician, who then provided a prescription for monotherapy with Oxytrol® TDS. These subjects may have been dissatisfied with their current treatment, wished to try a different route of administration, or were previously untreated. Subjects needed only one symptom to participate: urge incontinence, urgency or increased frequency. This six-month, use trial provided uncontrolled safety data for Oxytrol use in a prescription setting.

Subjects received an initial one-month supply of Oxytrol® with instructions for use. No subject had used Oxytrol® previously. Subjects were randomized into two cohorts: one received educational supplement materials in addition to the drug, while the other received nothing additional. At each evaluation point (1, 3 and 6 months), at least 90% of subjects reported rotating the patch. Re-supply and follow up visits occurred at the one, and three month marks when AEs were also recorded.

Most of the 2881 patients were female (87%) with a skew towards older age (median 63 years of age). Only half (49%) completed all six months of treatment. The most common reasons for early discontinuation were AEs (22% overall), consent withdrawn (7.9% overall) and lost to follow up (7.5%). Over 83% of the AEs leading to discontinuation were considered by the investigators to be drug-related, most frequently reported to be skin irritation or dry mouth.

The safety population included all subjects who received at least one dose of test drug. A total of 2834 AEs were reported by 1328 patients (46%). Over 50% were considered drug-related by the investigators. Adverse events related to skin irritation were the most commonly reported events, i.e., “application site pruritis” (n=142; 4.9%), “application site erythema” (n=131; 4.5%) and “application site dermatitis” (n=129; 4.5%). Subgroup analysis by age (≥ 65 years (47.5%), < 65 years (52.4%)) or gender showed a difference in the reporting of serious adverse events (SAEs) (2% of subjects < 65 years and 5.5% of those 65 or older). Older subjects tended to report slightly more skin (11.6% versus 10.4%) and gastrointestinal events (10.7% versus 8.2%). “Dry mouth” (n=84) was the most common anticholinergic-related event. Other anticholinergic-related events were “constipation” (n=58), “dizziness” (n=56) and “blurred vision” (n=36). Skin irritation events and dry mouth were the only AEs reported by $> 2\%$ of the trial population. There were 82 reports of “urinary tract infection” in 67 patients (three had UTIs diagnosed and treated at enrollment; nine had multiple UTIs). Five cases were serious and 5 subjects with UTI permanently discontinued the drug.

The sponsor’s report of this trial does not include details of subjects’ pre-enrollment symptoms or address if some subjects may have had symptoms more consistent with early UTI than idiopathic OAB (although, subjects with untreated UTIs were excluded from enrollment). It is notable that 10 subjects had UTIs diagnosed within the first week after starting test drug. Only one discontinued the trial due to UTI. Since no further narratives regarding the subjects’ pre-enrollment history of symptoms were provided in the report, it is difficult to assess whether the subjects’ initial OAB symptoms may have

been due to undiagnosed UTI. However, Sand et. al⁹ noted that most subjects in the trial had OAB symptoms for over two years (69.5%). They reported only 12% of subjects had symptoms for < 1 year, but do not further define symptom duration.

Reports of serious AEs were skewed towards older patients. In those > 65 years of age, 114 serious events were reported compared to 54 in those under 65, but older subjects had more comorbidities that could increase their risk of serious events. Older subjects were not more likely to discontinue the trial due to AEs. The most commonly reported preferred terms under “Infections and Infestations” (n=28) were “pneumonia” (n=8) and UTI (n=5). Preferred terms under “Nervous System Disorders” (n=26) and “Cardiac Disorders” (n=20) were also frequently reported, particularly “cerebrovascular accident” (n=7), “dizziness” (n=5) and “myocardial infarction” (n=7). Only one SAE, a UTI, was considered drug-related by the sponsor since the patient reported symptom onset just over one month after starting Oxytrol®. However, this 57 year-old female had a long history of recurrent UTIs, and the reporting physician did not feel the diagnosis was related to use of test drug. There were three deaths, two from cardiovascular causes and one from natural causes, all assessed as unrelated to drug. Overall, the frequently reported AEs appear consistent with those included in Rx labeling and proposed OTC labeling: skin irritation and anticholinergic effects.

The AE reports were also categorized by topics of special interest, UTI, pregnancy, urinary retention, urogenital malignancy, diabetes, and benign prostatic hyperplasia (BPH). These are diagnoses with symptoms similar to OAB. One hundred-ten events matched topics. The majority were UTIs (n=82) and urinary retention (n=10). Only one subject with urinary retention completed the trial. One urinary retention case also described a UTI and was considered serious (ID# 35101). An 86-year-old female reported back pain, increased frequency, and burning on urination. The timing of the symptoms was not provided. A urinalysis was consistent with a UTI for which the patient was hospitalized for antibiotic treatment. A bladder ultrasound done five months later, while the patient continued to use Oxytrol®, revealed large post void residual bladder volume. The reporting physician did not believe the symptoms were related to Oxytrol® use.

While there were 222 subjects who reported having diabetes pre-enrollment, 22 additional subjects reported diabetes-related signs such as hyperglycemia or glucose intolerance at enrollment. Eight of these subjects discontinued the trial due to AEs which were mostly skin-related, or due to dizziness, pain or fatigue. Seven subjects reported no improvement or worsening OAB symptoms during the trial. There were nine diabetes-related adverse events, but none were new diagnoses, and none led to discontinuation.

No pregnant subjects were enrolled in the trial, and there were no new pregnancies reported. There were 16 reports of falls leading to fractures and other injuries, though none were considered by the investigators as drug-related. A male patient reported BPH

⁹ Sand P, N Zinner, D Newman, V Lucente, R Dmochowski, C Kelleher, et. al., 2006, Oxybutynin Transdermal System Improves the Quality of Life in Adults with Overactive Bladder: A Multicentre Community-based, Randomized Study, *BJU Int*, 99: 836-844

nearly four months into the trial. He was diagnosed with prostate cancer three weeks later.

Adverse Event Database Reporting

The sponsor submitted a comprehensive postmarketing AE report for the Rx Oxytrol® transdermal system. The report included the following:

- Summary of International Postmarketing Safety Update Reports (PSURs) and Periodic Adverse Drug Event Reports (PADERS) from the NDA holder, Watson Pharmaceuticals, Inc. – **June 2003 (market launch) - February 25, 2012**
- Review of postmarketing safety from AERS (**January 1, 2003 – December 31, 2011**), WHO (**January 1, 2003 – April 30, 2012**), American Association of Poison Control Centers (AAPCC) databases (**February 1, 2003 – April 30, 2012**)
- Focused review of topics of special interest
 - Diabetes
 - Bladder cancer
 - Urinary tract infections
 - Pregnancy
 - Skin reactions
 - Anticholinergic AEs
 - Urinary retention
 - Narrow angle glaucoma
 - falls, disorientation, confusion
- Review of the scientific literature pertinent to safe use in the Rx setting (**1996 - April 2012**).
- The 120-day safety update was submitted on July 27, 2012. It included updates from the NDA holder’s pharmacovigilance database for Oxytrol® and Gelnique®, AERS, WHO, AAPCC and new reports from the scientific literature. No new clinical trials were undertaken or completed.

PSUR/PADER Review

Oxytrol TDS has been marketed in several foreign countries since August 2004. Nearly 9700 and 3750 reports, respectively, have been included in the PADERS (Periodic Adverse Drug Experience Reports) and PSURs (Periodic Safety Update Reports) since marketing began inside and outside the U.S. The sponsor notes that over 27 million patches have been distributed in the U.S. since 2003; about 40 million worldwide. In all, 13,190 AEs (96%) were classified as non-serious. While 595 AEs (4%) were considered serious, only 106 were labeled events. The sponsor considered dizziness to be the only SAE directly related to use of Oxytrol.

Over 32% of all AEs included reports of “application site erythema,” “application site pruritis,” or ineffectiveness. Over 5300 AEs (40%) described application site-related terms. In the PADERS, gastrointestinal disorders accounted for 11.5% of all reported AEs, with “dry mouth” (n=311; 3.1%) most frequently reported. This was the most common anticholinergic side effect and included in 99 (2.6%) reports within PSURs. Other possible and frequent anticholinergic effects included “constipation” (n=222),

“blurred vision” (n=252), “dizziness” (n=247) and “somnolence” (n=207). Nervous System disorders account for 7.7% of all reported AEs in PADERS, with dizziness-related events most common, followed by “fatigue.” Only 8 AEs were reported in more than 2% of cases submitted in PADERS (**Table 4**). No additional significant preferred terms were identified.

Reports from PSURs are combined from various international drug safety monitoring authorities. The number of reports may be overestimated due to duplication. Comments on the impact of these reported events, particularly application site reactions, anticholinergic effects and drug ineffectiveness will be addressed in the section on “AERS Reports.” As compared to common AEs reported across drug classes such as constipation, diarrhea, nausea, and abdominal pain, dry mouth is both relatively more frequently reported and more often reported with use of drugs with anticholinergic effects. The frequent reporting of application site reactions, and even drug ineffectiveness, can be addressed quite readily by consumers in the OTC setting. They may consider removing the patch and choosing an alternative drug.

Table 4: AEs Reported in PADERS with Frequency \geq 2%

Organ System Class	Preferred Term	Serious Unlisted	Serious Listed	Non-Serious Unlisted	Non-Serious Listed	Total Events	% of Total Events
	Total # AEs:	204	40	3,021	6,435	9,690	
General Disorders & Administration Site Conditions	Application site erythema	0	0	0	1416	1416	14.61%
General Disorders	Application site pruritus	0	0	0	1053	1053	10.87%
General Disorders	Drug ineffective	0	0	359	601	960	9.91%
Gastrointestinal Disorders	Dry mouth	0	1	0	303	304	3.14%
General Disorders & Administration Site Conditions	Application site rash	0	0	0	246	246	2.54%
General Disorders & Administration Site Conditions	Application site irritation	0	0	1	220	221	2.28%
Eye Disorders	Vision blurred	0	0	0	196	196	2.02%
Nervous System Disorders	Dizziness	1	1	156	28	186	1.92%

Source: Adapted from Applicant’s submission, Module 5.3.5.3, Integrated Summary of Safety, Section 3.5.2.1 Table 13, p. 74

Among serious adverse events, only 17 unlisted (unlabeled) events were reported more than three times. They include reports of “convulsions” (n=13), “confusional state” (n=9), “UTI” (n=7), “psychotic disorder” (n=6), “death” (n=5), and “cerebrovascular accident” (n=5) most frequently. Most other reports were single occurrences. The sponsor doubts that any of these SAEs are Oxytrol® related. The number of SAEs is small relative to all reported AEs and worldwide drug distribution.

A focused AERS search on AEs that may be associated with falls or injuries, particularly in older patients, i.e., “vision blurred,” “dizziness,” “somnolence,” “fatigue,” “confusional state,” and “asthenia. Three Standardized MedDRA Queries were identified that contain the above preferred terms plus others that may be associated with falls or injuries, “accidents & injuries,” “vestibular disorders,” and “hypotonic-hyporesponsive episode.” A search for terms in reports (February 2003 through July 2012) identified Oxytrol®, Gelnique® (oxybutynin topical gel) or transdermal patches not otherwise specified. There were 29 cases in total. Upon review, a sampling of cases follows:

- Three weeks after beginning Oxytrol® for overactive bladder, an 84-year-old female with history of atrial fibrillation began having dizziness and unsteady gait requiring assistance with walking. She was hospitalized and diagnosed with vertigo. Her physician related the symptoms to benign positional vertigo over use of oxybutynin.
- An 84-year-old female took Gelnique® for three days and began suffering dizziness (prior history), headache, fatigue and vertigo. She also had blurred vision and dry mouth. She described being “bed-ridden” for over one week due to the events.
- A 60-year-old female without significant past medical history was hospitalized after being found lying on the floor in a confused state. She had applied her first Oxytrol® patch the same day. She was somnolent, confused, and had difficulty speaking. Full physical, neurologic, including heat CT, and lab evaluations were normal. Her concomitant medications were Synthroid®, trazodone and clonazepam.
- A 67-year-old female without significant medical history was hospitalized for treatment of injuries from a fall. The reporting physician indicated that the patient had “global transient amnesia.” She had administered her first Oxytrol® patch three days prior to the fall. Concomitant medications included estrogen cream, zopiclone and mometasone nasal spray. The patient had previously used tolterodine for OAB without significant adverse events.

There did not appear to be any new safety signals based for the oxybutynin TDS on review of the SAE narratives provided by the sponsor. There were a few cases reporting injuries related to falls, but most of those reports did not include enough information to determine whether Oxytrol® use could be implicated. The reports also frequently list comorbidities with fall risks, e.g., neuropathies, joint replacements, vertigo, and concomitant medications that could be suspect, including clonazepam and zopiclone (not approved in the U.S.). These reports were frequently of elderly patients (average age=69 years (44-89)) who are at risk for falls for myriad reasons separate from use of Oxytrol®. However, in concert with reports of dizziness, sleepiness and confusion, risk of falls, with use of the drug in the elderly, is a concern.

The sponsor provided postmarketing safety data for Gelnique®, approved in 2009 for the same indication in a topical gel formulation. Two PSURs have been submitted. The dose of oxybutynin is higher and over a larger surface area than that for Oxytrol for Women®. Almost 1950 AEs have been reported for Gelnique® which has total

distribution of over 13 million doses in the U.S. The findings are similar to those reported with use of Oxytrol®, although reports of application site reactions are more common with Oxytrol®.

AERS Database

The FDA-AERS database contains spontaneous reports of AEs from a variety of sources. Interpretation of spontaneously reported AEs has several limitations:

- Reports are submitted voluntarily and the magnitude of underreporting is unknown.
- The reporting systems yield reporting rates, and not incidences.
- Clinical information is often limited in the reports, and causality can not often be determined.
- Duplicate cases are common, may not be removed, and may affect the impact of any further analysis.
- Reporting may be biased. A reporter's intent may confound the interpretation of associations between use of a drug and AEs. For example, a lawsuit or a publication may stimulate reporting.

A causal relationship between the use of oxybutynin, particularly Oxytrol®, and any particular AE or clustering of AEs is difficult to determine. An event may occur due to a subject's underlying disease, past medical history, concomitant medications or may be only coincidental in its temporal relationship to use of the drugs.

The sponsor estimates that over 27 million patches have been sold in the United States since market launch in 2003 through December 2011. Based on use of two patches per week, this equates to about 267,000 patient-years of exposure. Over two years of Gelnique® marketing, over 14.6 million doses have been sold. With daily use, this equates to about 40,000 patient-years of exposure. A total of 4279 AEs, identifying all forms of oxybutynin as suspect, are included in AERS. The sponsor excluded cases listing oxybutynin as concomitant with no relation to the reported event. A focused review was conducted on the Oxytrol® patch, Gelnique® topical gel, or reports indicating use of an unidentified transdermal patch. In total, there were 604 AEs associated with use of Oxytrol®. There were 116 AEs in reports identifying use of Gelnique®, and 81 cases reporting use of an unidentified oxybutynin transdermal drug product. Over 72% of all cases involve female patients. For Gelnique®, there were 10 SAEs reported in children 2-5 years of age for whom the drug is not indicated. No further information on these cases was provided by the sponsor.

The sponsor included AE data identifying oral forms of oxybutynin and oxybutynin not otherwise specified (NOS). The frequently reported events are common to all oxybutynin drug products. For skin-related AEs, only "rash" was reported more than 1% of the time, making it unlikely that transdermals were used to great degree. The safety profiles between oral and transdermal forms are quite different, and it is not possible to distinguish formulations in the NOS reports, this review focused on the identified transdermal forms.

The most frequently reported AEs were General and Administration Site disorders (n=140; 21%), Psychiatric disorders (n=81; 12%), Nervous System disorders (n=81; 12%) and Gastrointestinal disorders (n=53; 8%). Events accounting for more than 2% of all reports include only “drug ineffective” (n=29), “pharmaceutical product complaint” (n=13) and “application site erythema” (n=11). Other frequent, possibly oxybutynin-specific events, include “dry mouth,” “application site pruritis,” “dizziness,” “constipation,” “urinary tract infection,” and “vision blurred.” Most of these were reported 6-10 times each (1%). Application site reactions accounted for about 40% of all preferred terms (PTs) under General and Administration site disorders. The reported events are consistent with those included in the NDA holder’s database. Of those cases where age was reported, patients > 65 years old account for 42% of the total.

The most frequently reported SAEs (10 or more reports, or >1.7%) were drug ineffective, pharmaceutical product complaint, application site erythema, and fall. Nine others including dizziness and vision blurred were also more commonly reported.

It is unclear why so many reports are classified as serious that seem not to have significant safety implications, particularly “drug ineffective” and “pharmaceutical product complaint.” It is likely due to the sponsor focusing their review only on cases identifying oxybutynin as the primary suspect drug. Regardless, the reports do not identify any new safety signals that would prohibit use in the OTC setting.

WHO Database

The sponsor conducted a similar search as that described above for AERS data. The review period was January 1, 2003 – April 30, 2012. Only cases from outside the U.S. are reported here, assuming that U.S. cases are captured in AERS. A total of 2435 AEs, identifying all forms of oxybutynin, are included in the WHO database. Gelnique® is not marketed outside the U.S. Most of the cases report non-serious events. Oxytrol® or Kentera (the equivalent European tradename), or a transdermal NOS were identified in 362 reported events. Females accounted for the majority of reports (82%). In reports where age was included, near 60% of cases were in those >65 years of age; although, there were 27 reports (21 serious) in children under 17 years. The sponsor provides estimates of over 13.6 million patches distributed outside of the United States since marketing began in 2004. This equates to over 130,000 patient-years of exposure.

There are no further details on the 27 pediatric reports. Neither Oxytrol® nor Kentera are recommended for use by children under 18 years of age.

The most frequently reported AEs include General Disorders and Administration Site Conditions (n=102, 34%) followed by Skin and Subcutaneous Tissue Disorders and Gastrointestinal Disorders, 35 (13.6%) and 31 (12.1%) AEs respectively. Individual AEs that accounted for ≥ 2% (five or more) of the total include “drug ineffective” (n=36), “application site reaction” (n=12), “rash” (n=8), “nausea” (n=6), and “application site erythema,” “dizziness,” and “pruritis” (n=5 each). Other, anticholinergic-related events included “dry mouth” (n=4), “vision blurred” (n=3), and “somnolence,” “fatigue” or “sedation” (n=7). Additionally, there were several reports (n=8) that indicate falls or

increased risk for falls, i.e., “fall,” “muscular weakness,” “gait disturbance,” “accident at home,” “spinal fracture,” or “disorientation.” Of the total, 115 events (37.7%) were considered serious. “Application site erythema” was the most frequently reported preferred term.

Overall, the frequently reported AEs are consistent with known risks associated with proposed OTC use of Oxytrol for Women®. In the context of distribution and sale since worldwide marketing began, the number of reports is small. There are no new safety signals identified.

AAPCC Database

Data from this database was collected for the time period from February 1, 2003 through April 30, 2012. Overall, there were 67 cases captured that identified either Oxytrol® (n=27), Gelnique® (n=28) or oxybutynin NOS (n=12). Females accounted for 89%. Most reports were of unintentional exposures (66%). Five reports indicated that more than one patch or application, up to a maximum of four, was co-administered. There were 13 cases reporting exposure in children under age 18. There were 19 AEs reported. Pertinent effects, particularly those that may increase fall and injury risk, were confusion, dizziness/vertigo, and drowsiness/ lethargy, muscle weakness, numbness (n=12). The majority of medical outcomes were of minimal to moderate effects. Those with moderate to major effects were not further described. There were no new safety signals identified.

SAFETY SUMMARY – SAFETY TOPICS OF SPECIAL INTEREST

There are several medical conditions and diseases with symptoms that overlap those of idiopathic OAB. The sponsor’s consumer behavior evaluation attempted to determine whether consumers, who may have symptoms of such conditions or diseases, will appropriately choose to speak with their doctor first, or not select to use the drug. An inappropriate selection decision may delay diagnosis and treatment of a serious medical condition. Additionally, consumers may use Oxytrol for Women® when they are unlikely to benefit from its use, thereby exposing themselves to risks associated with transdermals and anticholinergic drugs. However, it is important to note that consumers with these conditions may also have OAB and, therefore, may benefit from use of oxybutynin. Also, consumers with other conditions are unlikely to have sustained improvement in their symptoms, and may stop use and see their doctor, as directed on the proposed OTC label.

This section of the review will focus on pre-approval and postmarketing reports identifying diagnoses of diabetes mellitus, UTI, bladder cancer and pregnancy. It will include further evaluation of reports of anticholinergic effects, urinary retention, narrow angle glaucoma and address reports of falls, confusion and disorientation.

Diabetes Mellitus

Type 2 diabetes accounts for a large percentage of the number of patients with diabetes in the U.S. The prevalence of diabetes, and pre-diabetes, increases with age. Some consumers with diabetes may have increased urinary frequency and increased thirst.

Others may have a more insidious, initially asymptomatic onset that may go undiagnosed for many years. Increased urinary frequency in diabetes is due to increased urinary output. Oxybutynin is unlikely to have a sustained effect since OAB symptoms are due to bladder detrusor muscle instability and not increased urinary output. It is important to determine whether there is a potential risk for delayed diagnosis of diabetes with use of the drug in consumers who have urinary symptoms associated with the disease. The sponsor proposes to address this issue in OTC labeling.

“Diabetes” was reported as an AE in two pre-approval, phase 2 trials, but no post-approval trials (see review of the MATRIX trial in section Postmarketing Safety Trials above). There were five reports (0.85% of subjects). There were very few reports of AEs related to diabetes (n=5 specifically identifying “diabetes”) in the postmarketing safety databases for Oxytrol®, Gelnique® or oral forms. There is no literature published over the last 15 years indicating delayed diagnosis of diabetes with presenting OAB-like symptoms.

Bladder Cancer

Bladder cancer, although relatively uncommon, occurs more often in older persons and in males (2.7:1). Symptoms of urinary frequency or urgency may occur based on the location and size of tumors. More often, hematuria, particularly painless and gross, is a presenting sign in patients with bladder cancer. Symptoms similar to UTI may also present initially. **Table 5** compares presenting symptoms among diagnoses that can mimic OAB.

Table 5: Comparison of Presenting Symptoms for OAB, Bladder Cancer and UTI

Presenting symptom	OAB	Bladder cancer	UTI
Urgency	Yes	Occasionally	Yes
Frequency	Yes	Occasionally	Yes
Urgency incontinence	1/3 of cases	Occasionally	Occasionally
Nocturnal frequency	Often	Rare	Often
Abdominal pain	No	Occasionally	Yes
Pain on micturition	No	Occasionally	Yes
Pyuria	No	Rare	Yes
Hematuria	No	Yes (micro or macro)	Usually micro

Source: Adapted from Table 1; Nitti V, S Taneja, 2005, Overactive Bladder: Achieving a Differential Diagnosis from other Lower Urinary Tract Conditions, *Int J Clin Pract*, 59: 825-830. Micro = microscopic; Macro = macroscopic or gross.

There were no bladder cancer cases identified in clinical trials conducted to support original approval, in postmarketing clinical trials, or in the AUS (CONTROL). There was one case of bladder cancer identified in AERS with use of transdermal oxybutynin.

Consideration of the above presenting symptoms in Drug Facts labeling may provide consumers with a reasonable algorithm to help determine whether Oxytrol for Women® is an appropriate drug for them. Microscopic hematuria will not be detectable in the OTC setting. There may be a slight risk of delay in diagnosis since it is possible that the action of oxybutynin will have an effect on the OAB-like symptoms of bladder cancer.

However, exclusion of males from use of the proposed product, and the rarity of typical OAB symptoms at first presentation in a consumer with bladder cancer may limit the risk of delayed diagnosis.

In the literature, Månsson et. al.¹⁰ analyzed the reasons for diagnostic delays in 343 bladder cancer patients in Sweden. Diagnosis often depends on the patient's and primary physician's response to early signs and symptoms. There were significantly more males in the cohort (77.3%) and most presented with macroscopic hematuria (71%). The authors reported on delays based on symptoms. The only symptom in common with OAB was "urgency," where 49 patients (14.3%) presented with that complaint alone leading to a median of 45 days of patient delay in seeking consultation, and 114 days of physician delay in seeking diagnosis. The median patient delay was 15 days (mean 141 days). The median doctor's delay was 62 days. All other presenting symptoms included isolated hematuria or pain, some combination including at least one of those symptoms, or non-urologic findings. The authors note that complaints of urgency were more common in advanced cancers ($p < 0.002$). It appears that delays in diagnosis of bladder cancer are not uncommon when presenting symptoms are only OAB-like. Delays appear to be quite long in duration from the time a patient presents until they are referred to a subspecialist. It did not appear that there was worsening of stage progression correlated with diagnostic delay, nor was there a significant change in survival. Bladder cancers are generally slow-growing. The authors theorize that urgency is often misinterpreted as caused by infection, leading to prescription of antibiotics first. Other articles generally support these findings. It does not appear that availability of oxybutynin in the OTC setting would increase the risk of delay of bladder cancer diagnosis.

UTI

UTIs are very common, particularly in women. They can frequently present with urinary frequency and urgency, but usually occur in an acute setting as opposed to OAB where symptoms are often chronic. They are more typically coincident with dysuria, pain or foul-smelling, cloudy urine. UTIs can be self-limited depending on the etiology, but if they progress to the upper tract, i.e., pyelonephritis, symptoms will also progress to fever, chills and flank pain. While untreated pyelonephritis can lead to long term renal damage, such symptoms should prompt professional medical evaluation and management. Typically, urgency and increased frequency are due to bladder irritation and inflammation. Oxybutynin may reduce some of the OAB-like symptoms, but clearly will not treat the etiology, nor manage other symptoms such as dysuria or pain.

In clinical trials to support original approval, there were several UTIs reported, but the sponsor considered the rates similar to the background rate in the general population. Additionally, subjects had been previously diagnosed with chronic OAB symptoms as a matter of enrollment in trials. Most subjects who did suffer UTIs appeared to quickly recognize the symptoms and sought medical evaluation.

¹⁰ Månsson Å, H Anderson, S Colleen, 1993, Time Lag to Diagnosis of Bladder Cancer – Influence of Psychosocial Parameters and Level of Health-care Provision, *Scand J Urol Nephrol*, 27: 363-369.

Data from PADERS and PSURs identified few UTI-related events (n=245; 1.8%). Of these, there were 13 SAEs. AERS and WHO data were non-contributory. Proposed labeling for Oxytrol for Women® warns consumers not to use the drug if typical UTI symptoms, i.e., dysuria, hematuria, cloudy urine, foul-smelling urine, or back or side pain are present. Such symptoms have a high likelihood of association with UTI. The label also specifically warns about UTIs and instructs consumers that symptoms of OAB should be present for at least three months before choosing to use oxybutynin.

Pregnancy

Urinary frequency and urgency are common in pregnancy. Other pregnancy signs and symptoms, younger age of women of childbearing potential and proposed label instructions and warnings about possible early pregnancy should be adequate to ensure that women who have OAB-like symptoms, but who may be pregnant, take measures to confirm the diagnosis. Proposed labeling includes instructions for women who may be pregnant. It includes a warning to speak to a health professional if pregnant or breastfeeding due to the Category B designation and lack of studies of the drug in pregnant women. These, plus the instructions that women should have at least three months of symptoms, likely minimizes any risk of delaying pregnancy diagnosis. Even if women with an early pregnancy choose to use the drug, the progression of pregnancy and the lack of persistent effect of oxybutynin on their symptoms will likely result in stopping use.

The sponsor provided safety data supporting distinction between OAB and early pregnancy. Pregnancy was an exclusion criterion in clinical trials supporting original approval. One pregnancy occurred in any clinical trials. One report in the literature indicated that over 50% of women in their study cohort had OAB-like symptoms in their first trimester¹¹.

An AERS search of oxybutynin within the Pregnancy and Neonatal Topics SMQ which included several PTs related to pregnancy and congenital anomalies. There were 39 cases, with several apparent duplicates. There were a few reported cases of early spontaneous abortion, one early neonatal death and anomalies such as cleft lip and palate. Some of these events are not infrequent, and the cases often reported concomitant medications and other medical diagnoses that could contribute to various anomalies or events.

Skin Conditions

Use of the prescription product is often associated with local dermal reactions. Such reactions account for the most frequently reported AEs in clinical trials and postmarketing experience. Published literature also shows trial subjects most frequently reporting skin reactions. Since 2003, over 4700 cases of skin-related conditions, with nearly 9700 AEs, have been reported. Over 66% were non-serious. Application site erythema and application site pruritis account for over 25% of all AEs. Most reactions

¹¹ Van Brummen HJ, HW Bruinse, G Van De Pol, APM Heintz, CH Van Der Vaart, 2006, What is the Effect of Overactive Bladder Symptoms on Women's Quality of Life During and After First Pregnancy, *BJU Int*, 97: 296-300.

are mild and resolve spontaneously once the patch is removed. Several warnings are proposed in the Drug Facts label, and the directions to rotate patch site placement and limit use to four days seem appropriate. True allergic reactions have been reported rarely.

Anticholinergic-specific Events

Dry mouth is the most frequently reported anticholinergic-related event with transdermal use. In clinical trials to support original approval, rates of dry mouth were similar between treatment (9.4%) and placebo (8.3%) groups. Several trials reported in the literature, and provided to support original approval of Oxytrol®, support safety related to anticholinergic-related AEs. Data from spontaneous reporting is described further above; however, of all anticholinergic-related events, very few were SAEs. The sponsor proposes only to include warnings in labeling for OTC use that would be useful to the OTC consumer to support safe use. Therefore, they propose including only those events that may impact safety, i.e., sleepiness, dizziness, and blurred vision. Other warnings, such as one for dry mouth, are not on the proposed label.

Urinary Retention

The sponsor considered whether acute urinary retention is a risk due to the anticholinergic activity of oxybutynin. This medical condition is considered an emergency requiring prompt treatment. Individuals who have retention will seek rapid medical evaluation. However, retention is rarer in women compared to men (1:13), with the most common etiology being benign prostatic hyperplasia (BPH). The sponsor did not identify any reports in the literature of urinary retention requiring medical intervention in women using oxybutynin or any other anticholinergic drugs for OAB. Additionally, there were no reports indicating any association between OAB and resultant urinary retention. There were no reports of retention in any of the clinical trials conducted to support the original NDA. See the section **Postmarketing Safety Trial** above for pertinent data from the MATRIX study. Relative to the distribution of drug units worldwide, postmarketing reports of urinary retention are few. Proposed labeling instructs consumers with urinary retention, described as an inability to empty the bladder, not to use the drug. Also, men are not proposed as users of the OTC product, further improving safety related to urinary retention risk.

Narrow Angle Glaucoma

The sponsor addressed whether consumers may be at risk of angle closure when using oxybutynin if they have narrow angle glaucoma. OTC drugs with anticholinergic properties, such as antihistamines, have glaucoma warnings that appear adequate for safe use in the OTC setting. The postmarketing safety does not indicate a risk, nor does the published literature, save for a single report of an 80-year-old woman with acute angle closure brought on by oxybutynin use in the prescription setting¹². Proposed labeling warns specifically against use if consumers have narrow angle glaucoma.

¹² Sung VCT, PG Corridan, 1998, Acute-angle Closure Glaucoma as a Side-effect of Oxybutynin, *BJU*, 81: 634-635.

Falls, Confusion and Disorientation

While the effects of use of anticholinergic drugs, i.e., sleepiness, dizziness, and blurred vision, may contribute to increased risk of falls, it is important to note that falls and injuries may be a separate risk of OAB symptoms, particularly in older patients who have urinary urgency¹³. Older persons are also more likely to have age-related cognitive impairment, co-morbidities and use concomitant medications that may increase their risk for various nervous system and psychiatric disorders.

This reviewer has commented on falls, confusion and disorientation in the context of anticholinergic-related effects. See the section **PSUR/PADER Review** above for further discussion of falls and injuries. The sponsor did not identify any reports in the literature describing significant risk for falls or injuries related to use of transdermal forms of oxybutynin. There also does not appear to be any signal indicating clinically relevant changes in memory, cognition or mental status with use of oxybutynin. There were a few reports in postmarketing databases, but none that indicate a new safety signal.

This reviewer searched PubMed for references of the effects of anticholinergic drugs on patient cognition, described as information processing and psychomotor functioning that enable humans to exist in their environment. The focus of the search was on safety. Thirty-five articles were identified. Of these, a few reports were interesting.

Wagg et. al.¹⁴ reviewed the data on cognitive effects of antimuscarinic drug use, including oxybutynin, in elderly patients with OAB. They noted that older persons are sometimes less likely to be prescribed drugs for OAB due to concerns about safety, tolerability and side effects in light of age-related cognitive deficits or early-stage dementia. Potential drug interactions or drug potentiation are also a concern as older persons may be on several drugs with anticholinergic properties. Also, patients with conditions such as Parkinson's disease and cerebrovascular ailments may be more susceptible to the drug's effects. This group summarized available data on cognitive impairment as it related to use of several OAB drugs, including oral oxybutynin. In one of their references, they commented on significant cognitive effects related to use compared to diphenhydramine and placebo in a small, randomized, double-blinded, controlled trial of 12 subjects¹⁵. In nearly 50% of cognitive tasks tested, oral oxybutynin users had decreased performance. Wagg et al. recommended that older users of drugs with anticholinergic properties consider the risk for initiation or worsening of existing cognitive impairment, particularly when considering oxybutynin as a reliever of OAB symptoms.

¹³ Thom DH, MN Haan, SK Van Den Eeden, 1997, Medically Recognized Urinary Incontinence and Risks of Hospitalization, Nursing Home Admission and Mortality, *Age Ageing*, 26: 367-374.

¹⁴ Wagg A, C Verdejo, U Molander, 2010, Review of Cognitive Impairment with Antimuscarinic Agents in Elderly Patients with Overactive Bladder, *Int J Clin Prac*, 64: 1279-1286.

¹⁵ Katz I, L Sands, W Bilker, S DiFilippo, A Boyce, K D'Angelo, 1998, Identification of Medications that Cause Cognitive Impairment in Older People: The Case of Oxybutynin Chloride, *J Am Geriatr Soc*, 46: 8-13.

Appendix 1 – Current Prescription Labeling

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) 10/2012

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: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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3	DOSAGE FORMS AND STRENGTHS	8.5	Geriatric Use
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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, and somnolence. 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.

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of OXYTROL: dizziness and somnolence. 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.

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

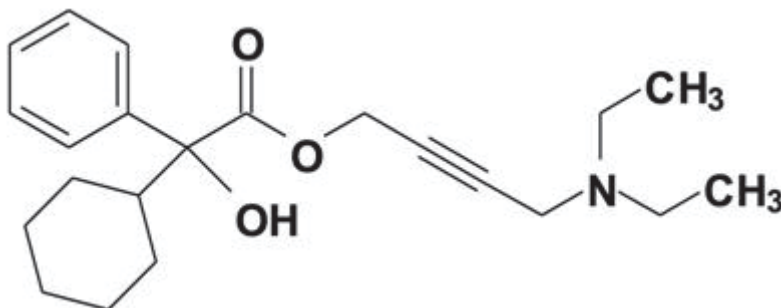
The plasma concentration of oxybutynin declines within 1 to 2 hours after removal of transdermal system(s). Patients should be monitored until symptoms resolve. Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac 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:

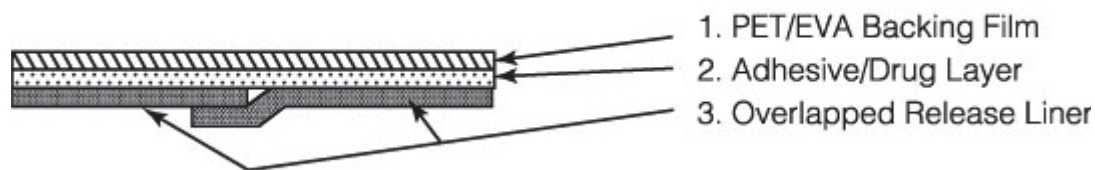


Oxybutynin is a white powder with a molecular weight of 357. It is soluble in alcohol, but relatively insoluble in water.

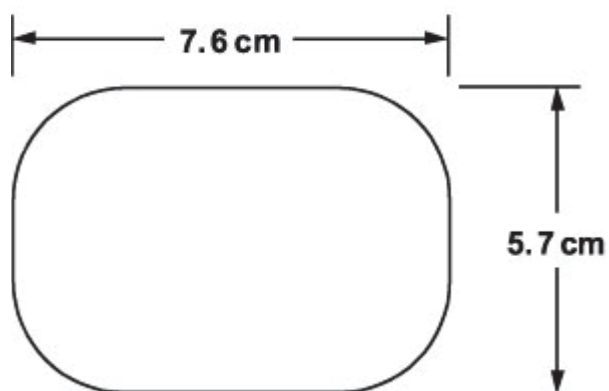
OXYTROL is a matrix-type transdermal system composed of three layers as illustrated in Figure 1. Layer 1 (Backing Film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 (Adhesive/Drug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

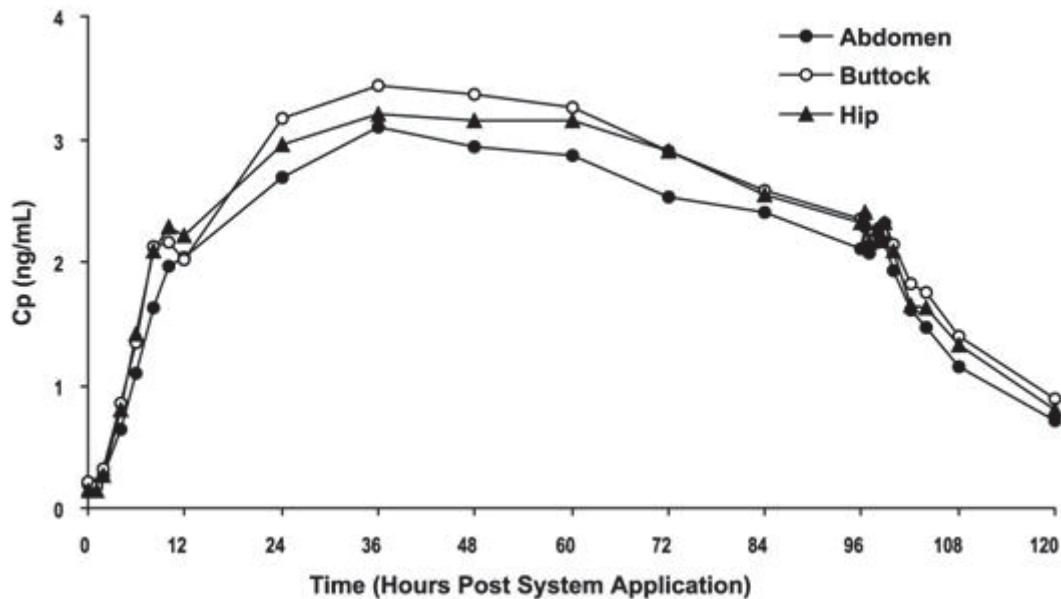
12.3 Pharmacokinetics

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.

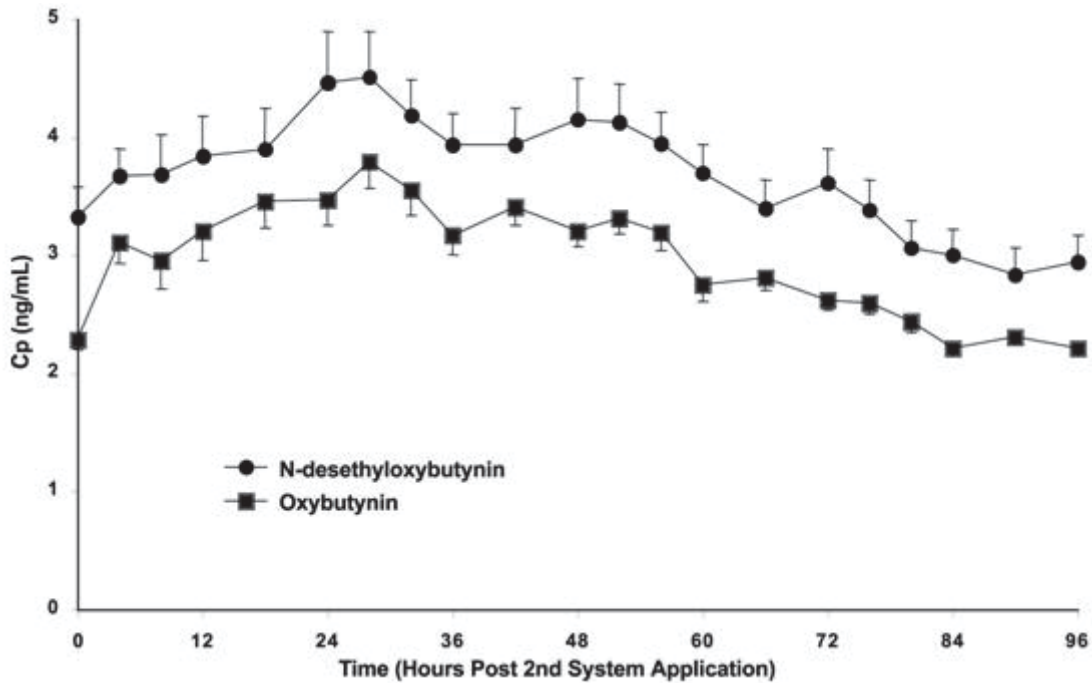


Table 3: Mean (SD) oxybutynin pharmacokinetic parameters from single and multiple dose studies in healthy men and women volunteers after application of OXYTROL on the abdomen.

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 AUC₀₋₉₆

⁴ 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.

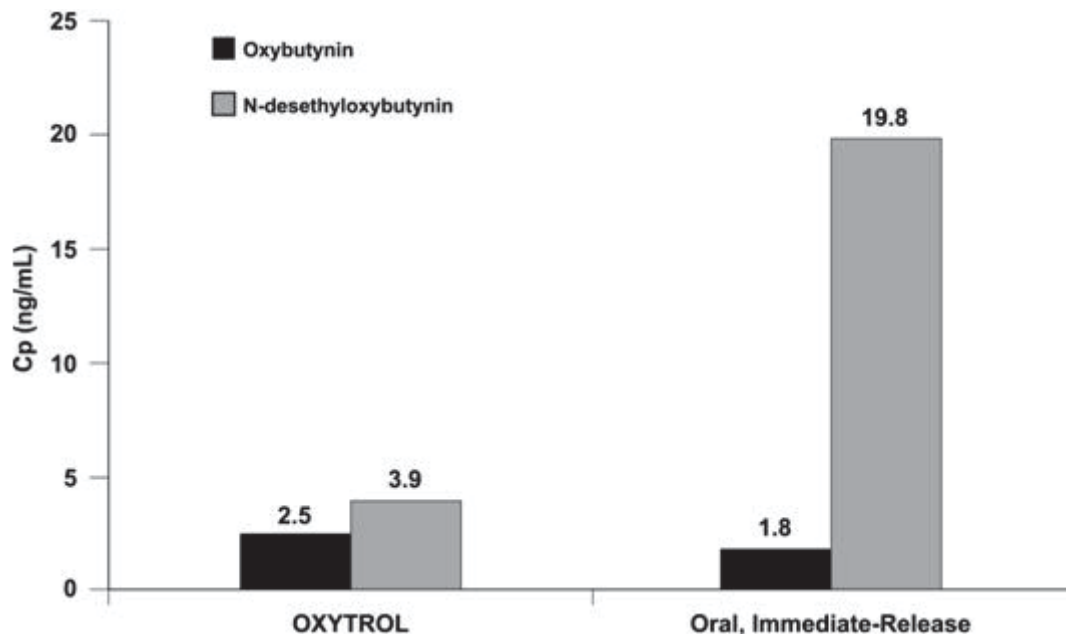
Metabolism

Oxybutynin is 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**	

*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*	

*Comparison significant if $p < 0.05$

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 clinical 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)

17.1 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.

17.2 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:

WATSON

Medical Communications

Parsippany, NJ 07054

800-272-5525

Distributed By:

Watson Pharma, Inc.

Parsippany, NJ 07054 USA

PATIENT INFORMATION
OXYTROL (oxe-tról)
(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-tről)
(oxybutynin transdermal system)

Read this Instructions for Use that come 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.

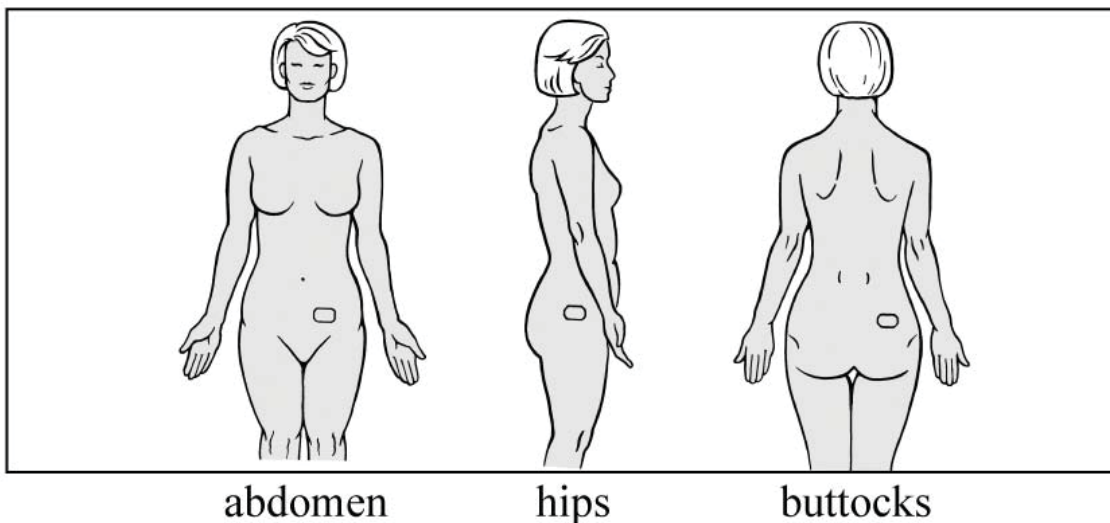


Figure A

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.**

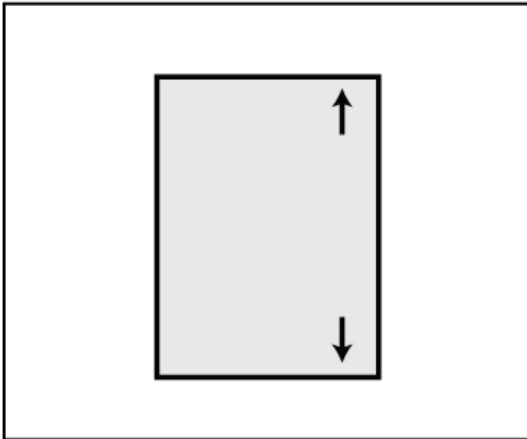


Figure B

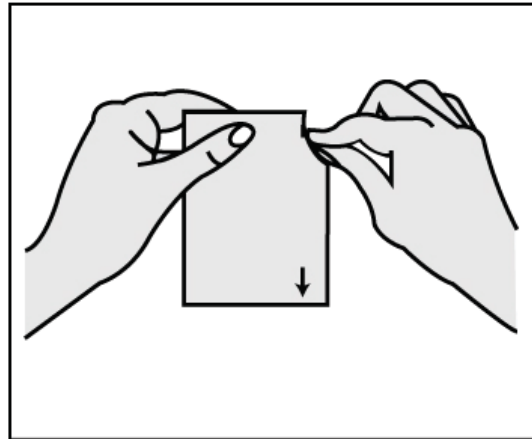


Figure C

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 side down, firmly onto the skin. **See Figure E.**

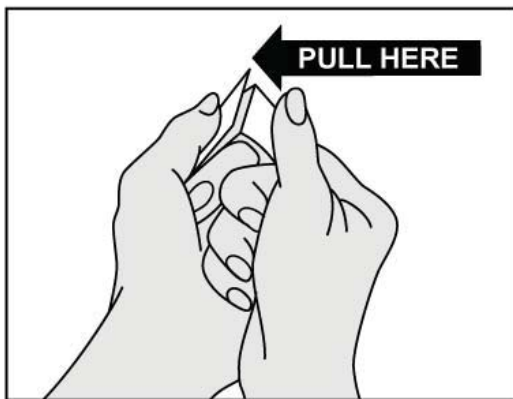


Figure D

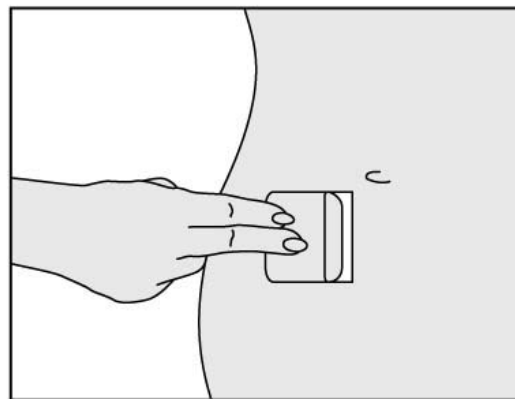


Figure E

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.

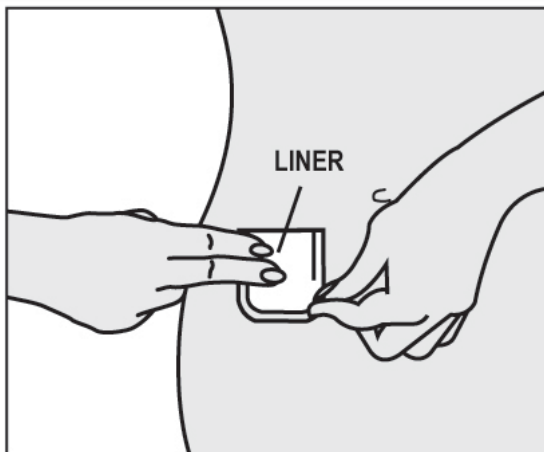


Figure F



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 Information Leaflet and Instructions for Use has been approved by the U.S. Food and Drug Administration.

For all medical inquiries contact:
WATSON
Medical Communications
Parsippany, NJ 07054
800-272-5525

Distributed By:
Watson Pharma, Inc.
Parsippany, NJ 07054 USA

Revised October 2012

Appendix 2 – Proposed Nonprescription Labeling



Drug Facts (continued)

Directions

- women 18 years of age and older:
- How to use the patch:**
- open individual pouch and apply immediately to a clean, dry and smooth area of skin on your abdomen, hips or buttocks. Do not put the patch on oily, damaged (cut or scraped), or irritated (rashes) skin. Do not put the patch on skin with oils, lotions or powders because that could keep the patch from sticking to your skin.
 - wear patch under clothing, do not expose the patch to sunlight
 - do not cut the patch into smaller pieces
 - wear only 1 patch at a time for 4 days in a row
 - after 4 days, remove the used patch and apply a new one
 - continue to change the patch every 4 days for as long as you use this product
 - each time you put on a new patch, you should change the place where you put it (*i.e., abdomen, hips or buttocks*) to avoid possible skin irritation
- How to dispose of a used patch:**
- when you take off a used patch, fold it in half with the sticky sides together
 - throw it away so that it cannot be worn or swallowed by another person, especially a child, or a pet

Other information

- product comes in individual sealed pouches, do not use if pouch is torn or opened
- store between 20° to 25°C (68° to 77°F)
- protect from moisture and humidity
- do not store outside the sealed pouch

Inactive ingredients

acrylic adhesive and triacetin delivered on a polyester/ethylene-vinyl acetate film

Questions or comments?

Call toll-free: 1-800-252-7484 between 8:00 AM and 5:00 PM Central Standard Time, Monday through Friday

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Oxytrol FOR WOMEN

New!

Full Prescription Strength
OXYBUTYRIN TRANSDERMAL SYSTEM 3.9MG/DAY
Overactive Bladder Treatment

Oxytrol FOR WOMEN

RELIEF FROM
Overactive Bladder

1 Patch Treats for
4 Days/4 Nights

4 PATCHES
16-Day Supply

Drug Facts

Active ingredient (in each patch)
Oxybutynin transdermal system 3.9 mg/day.....overactive bladder treatment

Purpose

- Use**
- treats overactive bladder in women
 - you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months:
 - urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
 - urinary urgency (a strong need to urinate right away)
 - urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

Warnings

Frequent urination can also be caused by:
 ■ urinary tract infections (UTI) ■ diabetes ■ early pregnancy ■ other more serious conditions
 If you think you might have one of these conditions, see your doctor before use.

Do not use if you

- have any of these symptoms, which could be the sign of a UTI or other serious condition. See your doctor as soon as possible if you have:
 - pain or burning when urinating. These symptoms may also be accompanied by a fever or chills.
 - blood in your urine
 - unexplained lower back or side pain
 - urine that is cloudy, or foul-smelling
- are male
- are under the age of 18
- only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
- have been told by a doctor you have urinary retention (are not able to empty your bladder)
- have been told by a doctor you have gastric retention (your stomach empties slowly after a meal)
- have narrow-angle glaucoma
- are allergic to oxybutynin

LIFT FLAP

Drug Facts (continued)

Ask a doctor before use if you have

- risk factors or symptoms of diabetes, such as:
 - a history of diabetes in your immediate family
 - excessive thirst
 - extreme hunger
 - increased tiredness
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

Ask a doctor or pharmacist before use if you are

- taking a prescription medication for overactive bladder
- taking a diuretic (commonly called water pills)

When using this product

- you may see mild irritation when the patch is removed, this usually goes away in several hours
- sleepiness, dizziness or blurred vision may occur
- drinking alcohol may increase sleepiness
- use caution when driving a motor vehicle or operating machinery

Stop use and ask a doctor if

- you are not able to empty your bladder (urinary retention)
- condition worsens, or if new symptoms appear
- condition does not improve after 2 weeks of use
- you have an allergic reaction to this product
- you have severe redness, itchiness or blistering at the site of application

If pregnant or breastfeeding, ask a health professional before use.
 Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

ATTACH LEGEND ON ALL DIGITAL MECHANICALS

STANDARD FORMAT
 Helvetica Condensed
 Variable horizontal scale adheres to 39 characters per inch

Drug Facts - 10 pt Helvetica Cnd, Bold Italic

Drug Facts (continued)
Drug Facts - 9 pt Helvetica Cnd, Bold Italic (continued) - 9 pt Helvetica Cnd.

Headings - 9 pt Helvetica Cnd, Bold Italic

Sub Heads - 7 pt Helvetica Cnd, Bold

Text - 7 pt Helvetica Cnd, minimum leading 7.5

Square Bullets - 4.5 pt Zaph Dingbats no compression

Border - 1 pt rule, 3/64" gap all around

Barline - 1 pt rule

Hairline - .5 pt rule

Certified by: eb

APO #: TBD
 02.16.12 eb

Appendix 3 – Label Used in Pivotal LCS and AUS

Drug Facts (continued)

Directions

women 18 years of age and older:

How to use the patch:

- open individual pouch and apply immediately to a clean, dry and smooth area of skin on your abdomen, hips or buttocks. Do not put the patch on oily, damaged (cut or scraped), or irritated (rashes) skin. Do not put the patch on skin with oils, lotions or powders because that could keep the patch from sticking to your skin.
- wear patch under clothing, do not expose the patch to sunlight
- do not cut the patch into smaller pieces
- wear only 1 patch at a time for 4 days in a row
- after 4 days, remove the used patch and apply a new one
- continue to change the patch every 4 days for as long as you use this product
- each time you put on a new patch, you should change the place where you put it (*i.e., abdomen, hips or buttocks*) to avoid possible skin irritation

How to dispose of a used patch:

- when you take off a used patch, fold it in half with the sticky sides together
- throw it away so that it cannot be worn or swallowed by another person, especially a child, or a pet

Other information

- product comes in individual sealed pouches, do not use if pouch is torn or opened
- store between 20° to 25°C (68° to 77°F)
- protect from moisture and humidity
- do not store outside the sealed pouch

Inactive ingredients

acrylic adhesive, polyester/ethylene-vinyl acetate film, siliconized polyester film, triacetin, USP

Questions or comments?

Call toll-free number: 1-888-804-1671 24 hours a day, 7 days a week

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 **OXYTROL®**

NEW!

— FULL PRESCRIPTION STRENGTH —

OXYBUTYRIN Transdermal System 3.9mg/day
OVERACTIVE BLADDER TREATMENT

 **OXYTROL®**
for women

RELIEF FROM OVERACTIVE BLADDER

ONE PATCH TREATS FOR
4 DAYS/4 NIGHTS

4 PATCHES
2-WEEK SUPPLY

 **OXYTROL®**

OXYTROL[®]

Drug Facts

Active ingredient (in each patch)

Oxybutynin transdermal system 3.9 mg/day..... overactive bladder treatment

Purpose

Use

- treats overactive bladder in women
- you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months:
 - urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
 - urinary urgency (a strong need to urinate right away)
 - urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

Warnings

If you need to urinate frequently it could be an early sign of pregnancy, diabetes, a urinary tract infection (UTI) or a more serious condition. If you think you could have one of these conditions, it is important to see a doctor before using this product.

Do not use if you

- are male
- are under the age of 18
- have **any** of the following symptoms:
 - pain or burning when urinating. These symptoms may also be accompanied by a fever or chills.
 - blood in your urine
 - lower back or side pain
 - urine that is cloudy or foul-smelling**these symptoms could be the sign of a serious condition and you should see your doctor as soon as possible.**
- only experience accidental urine loss when you cough, sneeze or laugh, you may have stress incontinence. This product will not work for that condition.
- have urinary retention (are not able to empty your bladder)
- have been told by a doctor you have gastric retention (your stomach empties slowly after a meal)
- narrow-angle glaucoma
- are allergic to oxybutynin

LIFT
FLAP

Drug Facts (continued)

Ask a doctor before use if you have

- a history of diabetes in your immediate family
- frequent urination with excessive thirst, extreme hunger or increased tiredness. These could be early signs of diabetes.
- unexplained weight loss
- a history of kidney stones
- liver or kidney disease

Ask a doctor or pharmacist before use if you are

- taking a prescription medication for overactive bladder
- taking a diuretic (commonly called water pills)

When using this product

- you may see mild irritation when the patch is removed, this usually goes away in several hours
- sleepiness, dizziness or blurred vision may occur
- drinking alcohol may increase sleepiness
- use caution when driving a motor vehicle or operating machinery

Stop use and ask doctor if

- condition worsens, or if new symptoms appear
- condition does not improve after 2 weeks of use
- you have an allergic reaction to this product
- you have severe redness, itchiness or blistering at the site of application

If pregnant or breastfeeding, ask a health professional before use.

Keep out of reach of children. If swallowed, get medical help or contact a Poison Control Center right away.

Caution: New Drug - Limited by Federal law to investigational use.