FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

Oxytrol® for Women
Oxybutynin transdermal system, 3.9 mg/day

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Merck Consumer Care

Available for Public Disclosure Without Redaction

MSD

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAPCC	American Association of Poison Control Centers
AE	Adverse event
ADA	American Diabetes Association
ADE	Adverse drug event
AUA	American Urological Association
BC	Bladder cancer
BDI	Beck depression index
CI	Confidence interval
CNS	Central nervous system
CONTROL	Consumer Trial of Oxytrol
CSR	Clinical study report
DM	Diabetes mellitus
EOT	End of treatment
FPI	First patient In
GP	General population
HCP	Health care provider
HRQoL	Health related quality of life
IIQ	Incontinence Impact Questionnaire
IND	Investigational new drug
ISS	Integrated summary of safety
KHQ	King's health questionnaire
LB	Lower bound
LC	Label comprehension
LL	Low literacy
LPO	Last patient out
MATRIX	Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin TDS
MCC	Merck Consumer Care
MID	Minimally important difference
N-DEO	N-desethyloxybutynin
NDA	New drug application
NL	Normal literacy
OAB	Overactive bladder
OTC	Over-the-counter
QoL	Quality of life
SAE	Serious adverse event
SE	Secondary endpoint
SOC	System organ class
SS	Self-selection
TDS	Transdermal delivery system
UDI	Urogenital distress inventory
UTI	Urinary tract infection
WLQ	Work limitations questionnaire

WOC	Women of childbearing potential
WPQ	Work productivity questionnaire

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1.0 EXECUTIVE SUMMARY

1.1 Program Overview

MSD Consumer Care, Inc., operating under the tradename Merck Consumer Care (MCC), submitted an NDA on March 26, 2012 with data supporting over-the-counter availability of Oxytrol for use by adult women to treat the symptoms of overactive bladder (OAB). This Briefing Document will outline the benefits and potential risks associated with OTC availability of Oxytrol® for Women (Oxybutynin Transdermal System [TDS], 3.9 mg/day) and review the comprehensive development plan that was implemented to demonstrate OTC suitability. It will also explain the reasoning behind the overall conclusion that, compared to current options women are choosing for self-management of OAB, minimal additional risk will occur as a result of this product being made available OTC while providing meaningful benefit to consumers. In addition, the OTC NDA reviewed the efficacy and safety supporting the initial NDA approval in 2003 and seen during post-marketing experience, demonstrating a safety and efficacy profile which is acceptable for an OTC medication. The totality of the evidence supports the conclusion that women with OAB can self-recognize and appropriately treat their symptoms with the Oxytrol patch.

The improved access allowed by OTC availability of Oxytrol will provide symptom relief with a much needed safe and effective pharmacologic option, without increasing the risk of unintended outcomes. Additionally, the plans for a multifaceted educational and support program will increase awareness of OAB and bladder health in general.

OTC treatment of OAB symptoms is consistent with other OTC switch paradigms. Conditions like allergy and frequent heartburn are chronic but intermittent and of varying intensity and individual perceptions. OTC medicines help reduce symptoms and allow people to experience an improved quality of life and participate in regular daily lifestyle activities.

1.2 Overactive Bladder: Prevalence and Impact on Quality of Life

OAB is an important public health issue with an estimated 17% of adult women in the United States, or just over 20 million, suffering from symptoms. (Gopal 2008, Muller 2010, U.S Census Data 2008). It is one of the most common chronic ailments experienced by women (U.S. Census Data 2008 and National Health Interview Survey 2009). OAB is a syndrome clinically defined by urinary urgency, with or without urge incontinence, and is usually associated with urinary frequency and nocturia (Sand 2006).

OAB may occur in women of any age. However, it is typically associated with aging, with increasing prevalence between the ages of 45 and 60. The median age of the OAB sufferer is approximately 52 years (Stewart 2003). While OAB is not life-

threatening, it is lifestyle-limiting and has a well-documented impact on health-related and overall quality of life (QoL) measures. Studies have demonstrated that:

- OAB can impact many aspects of daily living, resulting in a progressive decline in emotional, psychosocial, and physical functioning (Irwin 2005; Bradway 2008; Sexton 2009, Newman 2002, Sand 2006).
- When the condition deteriorates to the point where women are experiencing urge incontinence, the relative odds of developing new psychological distress are more than two-fold higher (Bradway 2008, deVries 2012).
- Individuals with the most severe OAB symptoms have a more than two-fold greater incidence of depression and anxiety as compared to the non-OAB population (Coyne 2008; Sexton 2011).
- In the workplace, otherwise productive women with OAB report an increased rate of job change, absenteeism, early retirement or loss of employment (Nygard 2005, Sexton 2009, Pizzi 2009).

1.3 Current Self-Management of OAB

While women are readily able to recognize the symptoms of OAB, most choose to manage the condition on their own, often employing a variety of lifestyle modifications, coping mechanisms, and reliance on absorbent products. Over one-third of women with OAB have never discussed their condition with their physician (Gallup OAB Study 2011 and Forbes OAB Study 2012). Of those seeking treatment, women wait an average of 6.5 years before discussing their problem with a healthcare professional (Gallup OAB Study 2011). In contrast, women visit a doctor within days when they are experiencing symptoms of urinary tract infection (UTI) (Gallup UTI Study 2011). This reluctance to initiate a conversation exists even though these women visit a doctor's office an average of 6.9 times per year for other medical conditions (Harris 2003).

1.4 Pharmacologic Features of the Oxytrol Patch

While there is no cure for OAB, Oxybutynin TDS provides moderate but meaningful symptom relief for many people with OAB. Oxybutynin, the active ingredient, has been available by prescription for over 30 years. It blocks the action of acetylcholine at receptors in bladder smooth muscle. OAB is often characterized by detrusor muscle instability or hyperreflexia. Cystometric studies show that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction (oxybutynin TDS package insert, provided in Appendix 10).

The oxybutynin TDS is especially well-suited for OTC availability, balancing efficacy and safety. It delivers oxybutynin continuously and consistently over a 3 to 4 day period when applied to the abdomen, hip or buttocks. Because the patch delivers drug directly into systemic circulation, first-pass gastric and hepatic metabolism is

bypassed. This avoids the metabolic path which occurs with oral oxybutynin when it is metabolized to produce the active metabolite N-desethyloxybutyin (N-DEO), which has been associated with a part of the anticholinergic side effect profile seen with oral OAB products. N-DEO levels are markedly lower with transdermal delivery which has improved tolerability. The twice weekly regimen and sustained lower plasma levels promote better adherence and avoid the peaks and troughs of active moieties seen with oral anticholinergic agents as they reach therapeutic concentration. Because of this improved delivery method, oxybutynin TDS has efficacy comparable to other FDA approved oral oxybutynin products with an improved anticholinergic side effect profile, despite skin irritation at the site of application.

Additional information can be found in Section 4 Overview of Oxytrol Drug Product and Pharmacology.

1.5 Clinical Efficacy and Safety from the Original Prescription Development Program

The oxybutynin TDS proposed for OTC approval is the same dose and formulation as that approved for prescription use to treat the symptoms of OAB. The original clinical development program to support FDA approval for prescription use of oxybutynin TDS in 2003 included two placebo controlled Phase 3 studies to evaluate efficacy. In these studies, oxybutynin TDS (3.9 mg/day) was associated with statistically and clinically significant reductions of OAB symptoms compared to placebo, including incontinence episodes, urinary frequency, and mean void volume. The effect of oxybutynin TDS was shown to be comparable to that observed with orally administered oxybutynin and tolterodine (4 mg/day).

Overall, oxybutynin TDS was well tolerated in clinical development. Application site erythema and pruritus was reported by about 7.9% and 17.8% of subjects, respectively. Less than 1% of application site reactions were reported as severe reactions. Skin irritation events are common with the use of oxybutynin TDS and represent the major class of adverse event experienced with use of this formulation. Many OTC products use patch formulations which some degree of dermal irritation. These are expected AEs and are addressed in product use instructions, which instruct individuals to vary the location of the patch, and in product safety information. Furthermore, most events are of mild intensity. Anticholinergic side effects were slightly more frequent than with placebo but substantially less than seen with oral oxybutynin and tolterodine suggesting better tolerability. The post-marketing safety profile has been consistent with that observed in clinical development and no additional safety signals have been observed. Overall, the safety experience with oxybutynin TDS is consistent with a high degree of safety and there are no serious concerns that might preclude OTC use.

Additional information can be found in Section 5 Review of Clinical Benefits (Efficacy and QoL) and Safety.

1.6 Oxybutynin TDS Improves Quality of Life

Treatment-related improvements in objective outcomes may not reflect subjective improvements in TDS on QoL symptoms or other aspects of the condition that matter most to the patient (Khullar 2006). Thus, the aforementioned placebo-controlled Phase 3 studies also evaluated the QoL impact of oxybutynin TDS using both the Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI). Both studies showed a significant positive effect compared to placebo on the IIQ total score at the end of treatment (EOT). For the UDI assessment, patient's QoL improvement was demonstrated by the reduced total UDI scores at EOT. Statistically significant improvement compared to placebo was observed in female patients in Study O99009. (Summaries of this data from the original Watson NDA are in Appendix 2).

Following initial approval of prescription oxybutynin TDS, a Phase 4 study (MATRIX) was conducted to measure the impact of oxybutynin TDS on QoL in a more general population within a naturalistic setting. The MATRIX study was a large-scale (n=2,878), open-label, multicenter, prospective, community-based trial where adults with OAB were treated for up to 6 months with oxybutynin TDS. Participants self-rated QoL on physical, emotional and social modalities at baseline, 3 and 6 months. A total of three instruments were used to measure QoL in this study:

1. The King's Health Questionnaire, a validated 27-item, 10-domain instrument used to assess symptoms and health-related QoL in participants with OAB
2. The Beck Depression Inventory a validated 21-item instrument used to assess the existence and severity of symptoms associated with depression.
3. The Work Productivity Questionnaire, a validated, 8-item, 4-scale instrument used to assess impairment of work activities and loss of productivity.

All QoL measures in this open-label study showed clinically significant improvements from baseline associated with oxybutynin TDS treatment.

Additional information can be found in Section 5.2.2.

1.7 Oxytrol OTC Development Program

1.7.1 Self-Management Labeling Safeguards

The main rationale for a product to be appropriate for use without direct involvement of a healthcare professional employs three basic approaches to risk reduction:

1. The consumer labeling must successfully direct a large majority of consumers to make a correct "self-selection" decision that the product is right for them. In this case, they are women with symptoms consistent with OAB and none of the medical conditions or situations which warn against use.

2. Once using the product, the label must successfully direct a large majority of users when to stop use (de-select) or consult a healthcare professional because of a change in medical status or lack of effect.
3. If the label is shown through study to be successful in guiding correct self-selection and de-selection, then only a very small cohort of users might use the product incorrectly. In this case, the inherent safety of the product and the clinical nature of any non-OAB condition they might have should not lead to unacceptable risks or outcomes.

With these tenets in mind, MCC first met with the FDA in 2007 to obtain guidance on the proposed Oxytrol OTC development plan and formulate the main elements of the Drug Facts label to be tested with consumers. MCC took the following approaches as a result of that discussion:

- The target population was limited to adult women. Men who have symptoms of OAB may require a prostate exam and should not use nonprescription Oxytrol without a professional recommendation.
- A prominent warning was added to the label to alert consumers that other conditions may also have urinary symptoms similar to those of OAB. These other conditions, although usually presenting with a constellation of symptoms, may also include urinary frequency and urgency (e.g., pregnancy, UTI, diabetes, or even bladder cancer). In such cases there may be a risk that use of OTC Oxytrol might delay professional diagnosis and/or treatment of the non-OAB condition.
- The label also instructs that OAB symptoms should be present for at least 3 months to reduce the risk that women do not use the product if they have more acute symptoms that may be associated with UTI or early pregnancy.
- The OTC label also includes a directive to seek medical care if no improvement is seen within a conservative 2-week time period, the earliest that women would start to feel an effect. While some clinicians find that a 2-week interval is adequate, others recommend 4 weeks or more

Thus, the OTC label helps women identify potential underlying disorders that could present with urinary symptoms. This provides a benefit not being offered on the absorbent products used by women who currently self-manage their OAB.

The proposed OTC label is provided in Appendix 9. Additional information can be found in Section 6.0 Overview of the Oxytrol OTC label.

1.7.2 STAGE I Self-Selection and Label Comprehension Studies

The OTC development program was an iterative process with FDA guidance throughout the program to develop an OTC label and measure its effectiveness in communicating important messages about the selection and usage of the product. Following the initial meeting with FDA in 2007, the first Oxytrol OTC package was developed and studied among consumers.

Additional information about the studies that follow can be found in Section 6.4. Stage 1 Initial Label Comprehension Testing aimed at measuring how well the label was understood in general and targeted populations. Self-selection studies assessed the decisions of targeted consumers on whether or not the product was appropriate for their use, considering their medical history and personal status.

1.7.2.1 Initial Label Comprehension Study (2008, Protocol 82023)

- Respondents demonstrated excellent comprehension of the product's use for treatment of OAB (96-100%) and showed strong understanding of OAB symptoms (83-91%).
- Recognition that symptoms of possible urinary tract infections or other more serious conditions preclude use also achieved high scores: blood in the urine (94%), lower back pain (91-95%) and pain when urinating (91-92%) were consistently understood. Males understood the message that the product is not for men (95%).
- Several messages attained lower scores than desired, notably narrow-angle glaucoma (77-83%), stress incontinence (73-81%) and developing blisters and itchy skin when using the product (79%).

1.7.2.2 Initial Self-Selection Study (2009, Protocol CL2008-19)

- All subjects had OAB symptoms and included normal literate (NL) and low literate (LL) cohorts of women as well as a third mixed cohort of adults with at least one of four key conditions: being male, having diabetes, having glaucoma, or being pregnant or breast-feeding. The self-recognition scores of 89% of NL subjects and 91% of LL subjects were consistent with that of the physician. Similarly, the self-selection decisions of 82% of NL subjects and 85% of LL subjects were consistent with the physician's assessment.

- While these scores are strong, review of the data from the subjects whose decisions were not consistent with that of a physician revealed that some subjects made one of two errors which carry little or no risk:
  1. The subject felt she did NOT have OAB or she should NOT use the product when the physician thought she did have OAB and/or could use the product. This inconsistency leads to no harm.
  2. The physician diagnosed stress incontinence rather than OAB. This inconsistency leads to minimal risk for the subject, since stress incontinence is a benign condition for which the product will not work.

When these factors are taken into consideration, the following conclusions can be drawn:

1. 95% or more respondents in the NL and LL cohorts made a self-recognition decision which was consistent with a physician or which was associated with minimal or no risk.
2. 92% or more respondents in the NL and LL cohort made a self-selection decision which was consistent with a physician or which was associated with minimal or no risk.

In Cohort 3, males attained a 72% score for correct self-selection, and the scores among respondents with diabetes, glaucoma, and pregnancy/breast-feeding were also not as strong as desired. Additional label changes and studies were undertaken to address those weaker results.

1.7.3 Stage II Self-Selection and Label Comprehension Studies

These above studies and the proposed labeling modifications below were discussed with the FDA at the End of Phase 2 Meeting in 2009.

- The name was changed from “Oxytrol” to “Oxytrol for Women," a female figure was featured prominently on the front label, and the package color was changed from blue to pink to better communicate that the product is not for men.
- The warning for diabetes was removed, since diabetes is not a contraindication on the Rx label. The message about undiagnosed diabetes symptoms was clarified.
- The warning about the urinary symptom which might indicate undiagnosed pregnancy, diabetes, and UTI was enhanced with stronger text and yellow highlighting.

In order to study the changes to the proposed OTC label and the results described above, a second stage of label comprehension and self-selection studies evaluated the modified Oxytrol OTC label.

Additional information about the studies that follow can be found in Section 6.6 Stage II Consumer Research Findings with Oxytrol OTC label.

1.7.3.1 Self-Selection Study in Men (Protocol 92061)

- 90% self-selected appropriately.

1.7.3.2 Label Comprehension Study in Women of Childbearing Age (Protocol 92062)

- 93% understood the enhanced pregnancy warning.

1.7.3.3 Self-Selection Study in Pregnant Women (Protocol 10054)

- 92% self-selected appropriately.

1.7.3.4 Label Comprehension Studies of Diabetes Messages (Protocols 92099 & 10053)

- A general population of women with OAB symptoms attained scores of 93-94%
- Respondents with some risk for diabetes scored 88-89%.

1.7.3.5 Label Comprehension Study in Women 65+ (Protocol 92101)

- Older women understood the directions for use and important safety warnings with nearly all important messages achieving 80% or higher understanding.

1.7.3.6 Pivotal Label Comprehension in Women with OAB (Protocol 10053)

- Most key messages were effectively communicated, meeting or narrowly missing their objectives. Actual scores were generally 87% and higher, with a number of important messages reaching 90% or more.
- The lowest scoring question (77%) occurred with stress incontinence, which is a benign condition for which Oxytrol will not work and therefore was a communication objective with lower medical consequence.

The results from this series of label comprehension and self-selection studies indicate that the label messages regarding directions for use and the key safety warnings are well understood by the broad target population as well as important cohorts. Thus, the label should effectively guide self-selection.

1.7.3.7 Actual Use Study - CONTROL

The modified label which was studied in the second stage of consumer research was also used in the actual use trial, CONTROL (CONsumer TRial of OxytroL). The objective of CONTROL was to evaluate ongoing use behavior in potential consumers. The CONTROL study was an observational open-label, 15-week study conducted in 10 metropolitan areas in the United States at 26 retail pharmacies. Telephone-based follow-up interviews and subject use diaries were used to collect product usage and adverse event data. All elements of each subject's observed behavior, including open-ended interview responses were applied to the determination of correct or incorrect decisions. The primary endpoint was the error rate for stopping use if new symptoms defined in the label (with the addition of abdominal and pelvic pain) occurred or if OAB symptoms worsened at two weeks. Pre-specified criteria for a successful study defined an upper confidence interval (CI) of $\leq$ 5.0%.

- A call center screened 2,731 potential subjects and 1,230 visited the site for an enrollment interview, of which 727 used Oxytrol to treat OAB symptoms.
- The primary endpoint was met. Of the 727 subjects, 3.4% of verified users failed to stop using Oxytrol when they should have based upon the label, with the addition of abdominal and pelvic pain (95% CI; 2.2%, 5.0%). The point estimate is determined through a data adjudication process called mitigation and is subject to medical interpretation in some cases. The findings were consistent by age, race, and literacy.
- Additional secondary endpoints examining consumer behavior also demonstrated appropriate ongoing use decisions, although some women reported that they needed longer than two weeks to assess whether or not the product was working for them.
- 98% of women who developed a UTI during the study acted appropriately.
- The safety experience was consistent with the approved prescription product labeling and no new adverse events of concern emerged in this 12-week Actual Use Trial. Patch irritation was the most commonly reported adverse event.

Additional details can be found in Section 6.7 CONTROL Study: Actual Use Testing.

1.8 Final Proposed Drug Facts Label

The proposed OTC Drug Facts Label for Oxytrol (provided in Appendix 9) encourages appropriate self-recognition and self-treatment of OAB. By encouraging women with potential undiagnosed UTIs, DM, BC, or pregnancy to see a health professional, the proposed OTC label is complementary with current clinical guidelines. Three key elements are included to minimize risks from underlying diseases that can produce OAB symptoms:

- The OAB symptoms should be present for at least 3 months.
- The OTC label encourages women with symptoms or risk factors for these other conditions to see a physician, providing an important benefit which may also improve earlier diagnoses and treatment of other potential underlying conditions.
- A two-week period for women to check response to Oxytrol treatment should minimize any risk of incorrect use. Assessing the effectiveness of treatment is based upon symptom response and consumers are able to recognize a lack of response to treatment without health professional involvement.

1.9 Bladder Health Education and Support Programs

MCC has developed a collaborative educational campaign working in conjunction with several prominent professional and consumer organizations such as American Urogynecologic Association, Nurse Practitioner's in Women's Health, National Association for Continence, Simon Foundation for Continence, Alliance for Aging Research and the Society for Women's Health Research, among others. These initiatives are designed to educate women that OAB is a treatable medical condition and not a natural part of aging. Women will be informed about both pharmacological options as well as behavioral strategies they can incorporate to improve their overall outcomes. These educational programs will be:

- Directed to consumers and healthcare professionals alike with the ultimate goal of increasing the comfort level of having open, honest communication about urinary health.
- Designed to reach a broad range of demographic and socioeconomic audiences.
- Multi-faceted and will include:
  - in-office and online brochures and quizzes to help make conversations between women and their healthcare providers easier
  - educational articles featured both in print and online
  - a public relations campaign including spokespeople to whom women can relate.

These programs are described in greater detail in Section 7.3.2.

1.10 Benefit and Risk Considerations for Nonprescription Access to Oxytrol

OAB is currently a condition which most women choose to self-manage. It is associated with a decreased QoL, an increased risk of depression, and reduced work productivity. Many OAB patients do not see physicians for treatment even when QoL is significantly impacted because they believe that OAB symptoms are simply another consequence of aging. Likewise, many women do not realize that OAB is a treatable medical condition. Due to the negative social stigma, shame and

embarrassment commonly associated with this condition, many women wait years after initial onset of OAB symptoms before deciding to discuss their symptoms with a healthcare provider. They choose instead to adapt their lives with a myriad of self-management strategies that can create substantial self-imposed restrictions on their lives.

Nonprescription Oxytrol will provide a convenient and effective treatment option for women currently managing with absorbent products and other restrictive self-management strategies. Although the effect size seen in placebo controlled studies is moderate, for those women who respond, Oxytrol represents a true benefit that will translate to symptom and QoL improvements. Additionally, nonprescription labeling and accompanying education and support programs will also increase awareness that urinary frequency can possibly be a symptom of other undiagnosed conditions such as UTI and diabetes. Ideally, this could even lead to earlier diagnosis of other conditions and overall public health may be improved as women gain more understanding and control of genitourinary health.

The availability of Oxytrol as an OTC product will not present any greater risk than already being incurred by women who self-manage OAB. In fact, it may actually have the potential to reduce consumer risk via responsible consumer education compared with the use of absorbent products and other OAB self-management strategies. The theoretical risks from making Oxytrol available OTC include a potential delay in diagnosis of UTI, DM, bladder cancer, and pregnancy. However, while urinary frequency and/or urgency can be present in all of these conditions, there are other more obvious clinical characteristics of these underlying diseases and conditions which are separate and distinct from OAB. Each of these conditions is discussed below.

1.10.1 Urinary Tract Infection

UTIs are characteristically acute in nature and present with painful urination, pressure, and sometimes hematuria, lower back pain, fever and/or cloudy/foul-smelling urine in addition to a sudden onset of urinary frequency/urgency. Appropriate, well-understood warnings on the label related to these symptoms, in conjunction with instructions to only use Oxytrol if OAB symptoms are present for at least 3 months, decreases the risk of confusing UTI and OAB. Using Oxytrol to treat an undiagnosed UTI will provide no relief of pain, hematuria, lower back pain, unusual looking/smelling urine, or fever, which, in addition to the numerous label warnings, should prompt a woman with these symptoms to seek appropriate medical care.

1.10.2 Diabetes

The American Diabetes Association (ADA) reports that about 26 million people in the United States have some form of diabetes, and about 7 million of these people are estimated to be currently undiagnosed (ADA Website). Type 2 diabetes (which is

the type most relevant to the potential Oxytrol target population) often goes undiagnosed because it has no symptoms or the symptoms seem benign. Most new cases of diabetes are found during routine health exams, not because a patient seeks help for a specific symptom. The Oxytrol label includes specific warnings of early diabetes signs including excessive thirst, extreme hunger, increased tiredness or a family history of diabetes. In addition, the special yellow-boxed warning alerts women that their urinary symptoms may be due to undiagnosed diabetes instead of OAB. The mistaken use of Oxytrol to treat the polyuria that women may experience with undiagnosed diabetes would provide no relief of symptoms. This, combined with the fact that many women are already managing urinary symptoms with absorbent products, strongly suggests that OTC access to Oxytrol would pose minimal, if any, additional new risk to delay detection of undiagnosed diabetes.

1.10.3 Pregnancy

Other than the obvious symptom of a missed menstrual period, early pregnancy signs may include spotting or a very light menstrual period, tender breasts, being tired, having an upset stomach or nausea, feeling bloated, frequent urination, and changes in mood (Rogers 2011). In addition, the highlighted warning combined with the directive to only use if symptoms have been experienced for at least three months, should effectively reduce the possibility that OAB could be confused with an undiagnosed pregnancy. Furthermore, consumer studies demonstrated that 93% of women of child-bearing age clearly understood the appropriate label messages, and 92% of pregnant women made an appropriate self-selection decision. Finally, it should be noted that any concern for confusion of OAB and pregnancy relates to the potential for delay in prenatal care rather than a risk to the unborn fetus. Oxybutynin is classified as a Pregnancy Category B ingredient, having not been shown to have teratogenic effects in animal studies or reported in post-marketing surveillance in over 30 years as a prescription product.

1.10.4 Bladder Cancer

The National Cancer Institute reports that the probability of developing bladder cancer (BC) in women between the ages of 50-70 is 0.32% (National Cancer Institute SEER Website). 17,910 cases of BC were diagnosed in women in 2012 and the five year 5-year survival rate is about 80% 2001-2007 (American Cancer Society 2012) suggesting a slow progression. The predominant symptom is visible blood in the urine. Other symptoms can also be similar to a UTI with painful urination, back pain, frequency or urgency. In addition to the highlighted warning on the label, there are appropriate, well-understood warnings on the label related to those other primary presenting symptoms, decreasing the risk of confusing a rare case of bladder cancer with OAB. Using Oxytrol to treat symptoms of an undiagnosed bladder tumor will provide no relief of hematuria, pain or lower back pain, which, in addition to the numerous label warnings, should prompt a woman to seek

appropriate medical care. Thus, there is little additional risk posed by the availability of Oxytrol as an OTC product compared to women who are already self-managing their OAB.

1.11 Overall Rationale Supporting Nonprescription Access to Oxytrol

OAB is a significant public health issue for women in the US and its prevalence is expected to grow as the population ages. While not life threatening, it has a detrimental impact on the QoL for the women who suffer. Embarrassment from episodes of incontinence and interrupted sleep from nighttime frequency often leads to social isolation, an increased risk of depression, and reduced work productivity. Despite women readily recognizing the symptoms of OAB, they do not see physicians for treatment even when QoL is significantly impacted. This is often because they believe that OAB symptoms are a consequence of aging and do not know it is a treatable medical condition. Due to the negative social stigma, shame and embarrassment commonly associated with this condition, many women wait years after initial onset of OAB symptoms before deciding to discuss their symptoms with a healthcare provider. They choose instead to adapt their lives with a myriad of less than optimal self-management strategies that can create substantial self-imposed restrictions on their lives.

The Oxytrol Drug Facts label will enable women, many who have had the condition for years, to correctly recognize and better self-manage their OAB symptoms. The warning in the Drug Facts label to stop use within 2 weeks if symptoms fail to improve also reduces the risk of any delay in treatment for any underlying conditions which may also cause urinary frequency or urgency.

Self-selection, label comprehension and the findings from the CONTROL actual use study affirm that the label effectively helps women to self-recognize OAB appropriately and decreases risk of mistaking an underlying condition for OAB. In CONTROL, 96% met the primary endpoint and 98% who developed a UTI reacted appropriately.

In conclusion, approval of nonprescription Oxytrol will provide a favorable benefit with minimal risk impact on public health by:

- Eliminating a barrier to access to an effective and safe medication which can help to reduce debilitating chronic symptoms that cause a reduction in quality of life. Not all users will respond, but for those that do, the symptom relief provided is meaningful and is associated with improved QoL.
- Increasing overall awareness of OAB and reducing the extent of under-treatment.
- Providing labeling and education efforts which will help women understand other potential causes of urinary frequency and encourage earlier treatment of conditions that can produce OAB-like symptoms.

- Allowing women an effective option to help them better self-manage their OAB, improve bladder health awareness, and encourage professional involvement when needed.

2.0 RATIONALE FOR NONPRESCRIPTION OXYTROL

OAB is a syndrome characterized by urinary frequency, urgency, and urge incontinence. In the United States, OAB is one of the most common chronic diseases in women, with a symptom prevalence rate in women of about 17%. Overall in the US only about 1.5 million are prescribed medications to treat OAB symptoms. Even initial OAB symptoms can have significant impact on QoL by interfering with the patient's ability to leave the home for employment or social engagements that require more than an hour or two without access to a bathroom. Because of the large degree of under or no treatment, there is significant unmet medical need among American women with OAB. Most women choose to manage the condition on their own and could benefit from safe and effective treatment option.

Prescription pharmacologic treatments for OAB, including fesoterodine, solifenacin, and oxybutynin primarily produce anticholinergic relaxation of the detrusor muscle. Oxybutynin is a competitive antagonist of acetylcholine at postganglionic muscarinic receptors that produces relaxation of bladder smooth muscle cells, a well-defined mechanism of action. Cystometric studies in patients with OAB characterized by detrusor muscle instability or hyperreflexia, show that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction.

The Oxytrol transdermal system, approved by FDA in 2003, produces consistent plasma concentrations of oxybutynin over a 3 to 4 day dosing interval. The maximal active moiety concentration with oxybutynin TDS is significantly less than with oral dosing and, because first-pass hepatic metabolism is avoided, there are lower concentrations of the active metabolite (N-desethyloxybutynin, N-DEO) which is associated with anticholinergic side effects. By delivering oxybutynin directly into systemic circulation via skin application (with related irritation side effects) and bypassing first-pass gastric and hepatic metabolism, the oxybutynin transdermal system is able to:

- improve tolerability,
- promote better compliance,
- avoid the peaks and troughs commonly seen with oral agents as they reach therapeutic concentration and,
- have more favorable anticholinergic adverse event profile than oral oxybutynin with efficacy comparable to other FDA approved oral oxybutynin products.

Before proceeding with OTC development, Merck evaluated the theoretical benefit and risk of nonprescription access to Oxytrol. This initial evaluation of benefit and risk provided the foundation for developing the Drug Facts OTC label for subsequent testing in consumer studies. This section outlines a framework for considering the benefit and risk evaluation of nonprescription Oxytrol. In addition, Sections 3 and 4 provide some background on OAB and oxybutynin TDS and Section 5 reviews clinical benefits (efficacy and QoL) and safety.

2.1 Evaluating Benefits and Risk of Nonprescription Products

Given the pharmacodynamic, efficacy and safety profiles of oxtbutynin TDS, the degree of overall benefit from nonprescription access depends upon the characteristics of OAB, how it is currently treated in the population, and the impact of Oxytrol on the consumers who use it. Limiting availability of drugs, biologics and devices to prescription only is necessary when the symptom, disease or condition for treatment requires assessment by health professionals to diagnosis the condition, select candidates for treatment, or to monitor the course of treatment. Hence, the benefit-risk assessment of nonprescription drugs effectively starts with the question of whether health professional involvement is necessary in the treatment of the symptom, disease or condition with the drug of interest. If not, then the net benefit to public health for access to nonprescription drugs is the balance between the benefits that accrue because of easier access against the rates of misuse, poorer clinical outcomes and other potential risks (Brass 2011).

In general, nonprescription access to a drug can provide a range of individual patient and public health benefits which can each significantly impact morbidity and improve quality of life. Easier access to nonprescription drugs may reduce the extent of under treatment, or a “treatment gap” in the general population. Additionally, improvement in clinical outcomes may result particularly when earlier treatment directly reduces morbidity and, in some cases, mortality. Improved consumer or caregiver understanding of the underlying disease, influenced by the content of the OTC label, may increase patient involvement in health care decisions leading to overall improvement in public health.

Because an evaluation by a health care professional is not required to obtain nonprescription drugs, there are potential risks from easier access that can adversely affect patient and public health if consumers deviate considerably from label directions. Risk occurs from the potential for improper recognition of the condition or failure to recognize and, if necessary, obtain treatment for an adverse event that develops during initial therapy. Intentional misuse for treatment of the condition or intentional misuse for other purposes may occur. Accidental ingestion or intentional overdose may be more likely with a change from prescription to nonprescription access if expanded access leads to more medication stored in consumer homes.

Eliminating prescribing by health professionals and interactions with the pharmacist may be reasonable given that the degree of benefit from expanded access is expected to be significantly greater than the risks that would not ordinarily be present when access is limited to health professional prescribing.

2.2 Potential Benefit of Nonprescription Oxytrol

MCC considered potential benefits and risks from making Oxytrol a nonprescription medication for OAB before starting OTC development.

Potential benefits of non-prescription Oxytrol to women with OAB include:

- A reduction in under-treatment by providing easier access to an effective therapy for women who are already self-managing their OAB.
- Earlier identification and treatment of conditions that can potentially share a symptom of OAB.
- Increased involvement of women in their own genitourinary care.

Some benefits are indirect, resulting from the risk reduction strategy that forms a significant part of the proposed OTC label. Urinary frequency and urgency can be caused by UTI, DM, and bladder cancer. The label was designed to inform women of the signs and symptoms of these conditions in order for women to accurately diagnose their symptoms as most likely due to OAB and therefore reasonable to treat with Oxytrol. Thus, an indirect benefit results if education leads women with undiagnosed conditions to seek health professional treatment.

2.3 Potential Risks of Nonprescription Oxytrol

The most important potential risk, other than the low incidence of side effects, including skin irritation, is as follows:

Improper self-recognition when symptoms are caused by an underlying condition which may delay diagnosis and treatment of that condition.

2.4 Weighing the Benefits against the Risks

The main rationale for a product to be appropriate for use without direct involvement of a healthcare professional employs three basic approaches to risk reduction:

The consumer labeling must successfully direct a large majority of consumers to make a correct “self-selection” decision that the product is right for them. In this case, they are a woman with symptoms consistent with OAB and none of the medical conditions or situations which warn against use.

Once using the product, the label must successfully direct a large majority of users when to stop use (de-select) or consult a professional because of a change in medical status or lack of effect.

If the label is shown through study to be successful in guiding correct self-selection and de-selection, then only a very small cohort of users might use the product incorrectly. In this case, the inherent safety of the product and the clinical nature of any non-OAB condition they might have should not lead to unacceptable risks or outcomes.

Current clinical guidelines recommend a urinalysis for women presenting to their physician with OAB symptoms. OTC labeling helps to screen for UTI by directing women with associated symptoms such as dysuria, hematuria or back pain to see a health professional. Likewise, requiring OAB symptoms to exist for at least 3 months before treatment will reduce the likelihood that acute UTI or early pregnancy is responsible for causing OAB symptoms. Finally, the recommendation in OTC labeling to terminate Oxytrol if there is no response or if symptoms worsen within two weeks, while conservative considering full effect could take 4 or more weeks, was designed to decrease risk of incorrect diagnosis since these other causes would not be expected to respond to oxybutynin.

Given the benefits from expanded access, MCC entered OTC development with the objective to demonstrate that the benefit/risk evaluation favors nonprescription access for Oxytrol. MCC also concluded early in development that it was feasible to develop OTC labeling that was supportive of the current clinical guidelines for OAB. In fact, the label educates women about the signs and symptoms of these other diseases, directing them to see a health professional for such symptoms.

This briefing document will discuss the issues in more detail. The overall rationale for OTC access is an improvement in public and individual health with labeling that minimizes potential for risk by:

- Focusing the indication to women
- Requiring symptoms for at least 3 months
- Recommending discontinuation if no response or worsening occurs within the first 2 weeks of therapy
- Recommending professional guidance when symptoms suggest possible UTI, diabetes, pregnancy or bladder cancer

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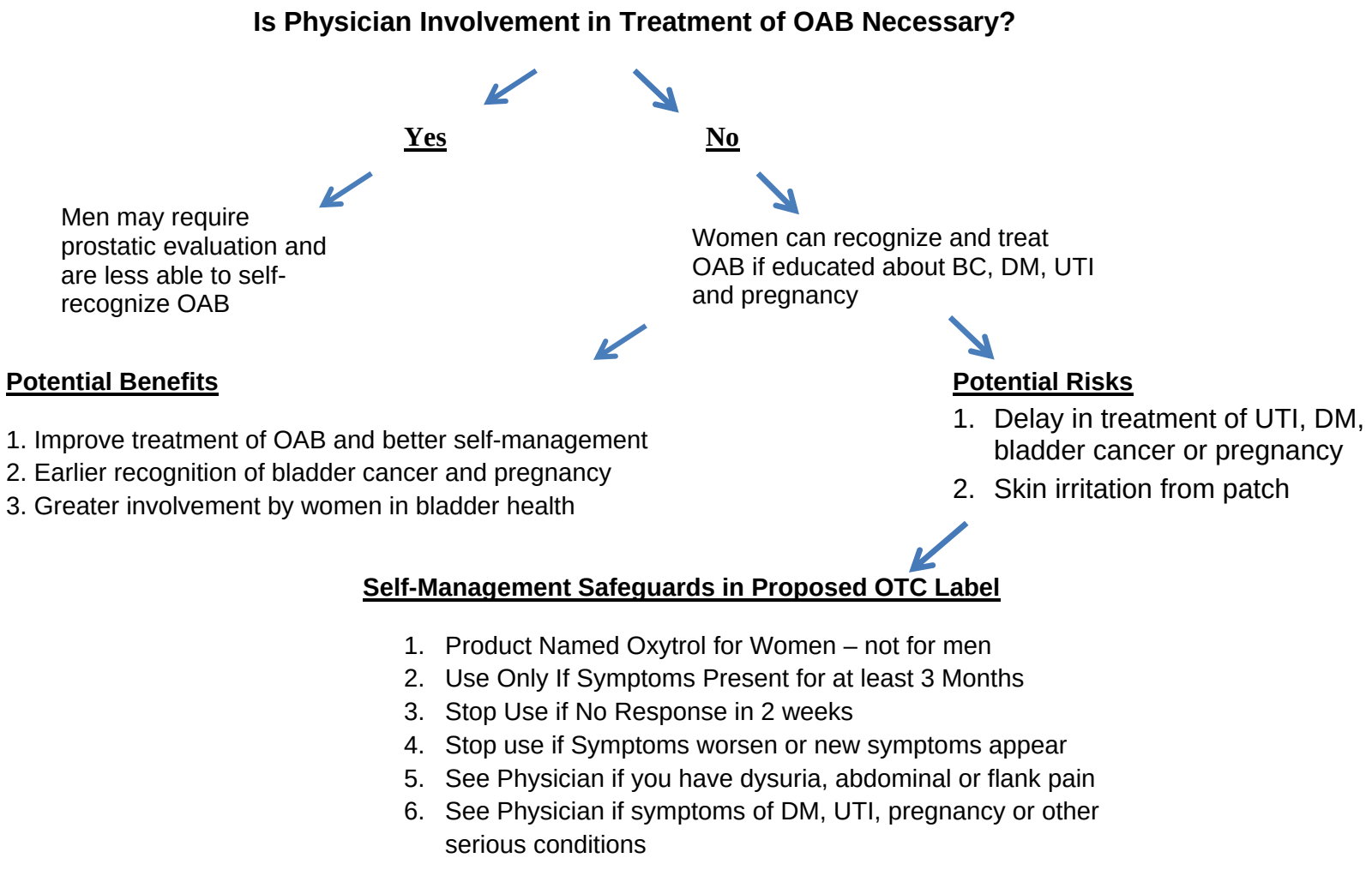
Figure 1 Oxytrol Labeling Safeguards Paradigm



3.0 OVERVIEW OF OAB

3.1 Self-Management is the Norm and Overall Impact is not Appreciated

As stated previously, OAB is a very common condition that, while benign in nature, has a negative impact on QoL. Self-management is the norm today and because of this large degree of under or no treatment, there is significant unmet medical need among American women with OAB for access to an effective medication.

Conversations are not occurring between patients and their healthcare providers, for many years, if at all. This delay in effective treatment may lead to a greater reduction in QoL.

A recent research study on women's attitudes and awareness of OAB (Overactive Bladder Attitudes & Usage and Segmentation, Forbes Consulting, July 2012) revealed that the primary reasons these conversations do not occur are due to their downplaying the impact OAB has had on their lives:

"I thought it was a part of getting older"

"I have more important health issues to worry about"

"It's not bad enough to talk with my doctor"

"I didn't think anything could be done"

"My doctor never asked if I had a problem with OAB"

This same survey also showed two-thirds of women have never tried a pharmacological product for their OAB, and of these non-users, 61% stated that they were not aware that these options exist. This figure is similar to the number reported over a decade earlier in another survey of women with OAB symptoms, where 56% stated they were not aware that effective treatments were available (Milsom 2001). Among patients who did discuss OAB symptoms with a health professional, 91% reported initiating the conversation rather than the doctor even though, on average, they are in the physician's office nearly 7 times a year for other medical conditions (Harris 2003). Considering that physicians have limited time with each patient and that they focus on those conditions that are of greatest medical concern, it is not surprising that OAB may not often arise during visits. In addition, the Forbes study also reported that, of the patients who did discuss the problem with the health care provider (HCP), 7 out of 10 felt their HCP did not take their condition seriously.

The economic burden of OAB is multifaceted, comprised of direct medical costs (i.e., drug therapy, in/outpatient care, labs, emergency room visits, and co-morbidities); non-direct medical costs (i.e., panti-liners, pads, diapers, and skin protection); indirect costs (i.e., work productivity, unemployment), and the aforementioned intangible costs (i.e., quality of life, psychosocial burdens) (Onukwugha 2009). The financial toll of OAB, like the condition itself, is frequently overlooked, either due to a

lack of consideration of the actual burden of the condition or the fact that available OAB cost assessments have been insufficiently comprehensive.

More recently, however, Ganz et al (2010) conducted a novel cost analysis utilizing a robust set of data incorporating direct and non-direct medical and indirect costs of OAB elucidated on age- and sex-specificities, inclusion of patients under the age of 40, and the effects of depression. The results of this comprehensive evaluation demonstrated the total overall national costs of OAB to be $65.9 billion ($1,925 per capita, including men; [Ganz 2010]). Factored into this estimate is worker productivity, where performance indicators often dictate retention. In fact, OAB has been directly linked to excessive absenteeism and presenteeism (coming to work when ill or not being able to function at full capacity) rates (Kannan 2009) as well as early retirement and job loss, resulting in a national financial burden in excess of $2.6 billion annually (Onukwugha 2009). Left unchecked within an aging population, with the concurrent increase in the condition's prevalence, the total economic burden of OAB in the United States is projected to exceed $76 billion by 2015 and $82 billion by 2020 (Ganz 2010). Yet many employers are unaware of OAB or its impact on their workers, in part because they see it as a condition that affects only much older people (Pizzi 2009).

3.2 Self-Management Strategies: Concealment and Lifestyle Restrictions

Anecdotal evidence gained through in-depth interviews with women who have self-reported OAB suggests that an overwhelming majority of women with OAB go to great lengths to develop ways to adapt to and conceal their symptoms. These strategies include heavy reliance on absorbent products, always making sure they are near a toilet ("toilet mapping"), foregoing activities they formerly enjoyed like walks, tennis, golf, the movies or social outings with friends, restricting fluids, and always being aware of types of clothing they wear or furniture they sit on. In short, this seemingly benign condition pervades every waking moment, and the woman with OAB never feels fully relaxed due to fear of an embarrassing accident or the odor associated with absorbent products. The learning gained through these extensive personal interviews is also supported and validated through numerous published studies. Data from other studies also show that the majority of women use absorbent products for OAB-related incontinence (Shaw 2001, Marshall-Kehrel 2006, Bradway 2007, Milsom 2001). These coping mechanisms may seem to only have impact on life quality. However, this approach may also lead to more serious health implications. Women with OAB have a statistically higher incidence of depression, poor sleep quality and UTIs due to use of absorbent products together with a sedentary lifestyle that may lead to other health consequences.

Just as there are misperceptions among many women (56%) that there are no effective treatments available for their OAB condition (Milsom 2001), clinicians also often underestimate the impact OAB has on the lives of their patients. Many physicians also have misperceptions that OAB is a natural part of aging or believe that treatments are generally ineffective. In short, health care professionals

frequently fail to consider the complications and co-morbidities associated with this common condition. (Milsom 2001, Ricci 2001)

3.3 OAB Impact on Quality of Life

OAB has a profound impact on health-related and overall quality of life. Data show that OAB touches virtually every aspect of daily living, resulting in a progressive decline in emotional, psychosocial and physical functioning (Irwin 2006, Bradway 2008, Sexton 2009, Newman 2002, Sand 2006). Women with OAB describe feeling vulnerable, powerless and humiliated. When the condition deteriorates to the point where they are experiencing urge incontinence, data show that the relative odds of developing previously undocumented psychological distress is more than two-fold (Bradway 2008, deVries 2012). Often this distress results in depression and anxiety and individuals with the most severe OAB symptoms have a more than two-fold greater incidence of depression and anxiety as compared to the non-OAB population. (Coyne 2008, Sexton 2011)

The impact of this condition on a woman's life is also evident in their sexual, physical and work limitations. Women with OAB are three times more likely to experience sexual dysfunction and this has been directly linked with deteriorating marital relationships (Vats 2008).

Self-imposed limitations on social interactions and physical activities not only take an emotional and psychological toll but a physical one as well. In fact, women with severe, incontinent OAB are 2.64 times more likely to be insufficiently active. In the workplace, otherwise productive women report an increased rate of job change, absenteeism, early retirement or loss of employment due to their OAB condition. (Nygaard 2005, Sexton 2009, Pizzi 2009)

Despite this negative impact on health-related and overall quality of life, OAB remains largely undiagnosed and untreated. This situation exists because the current health care paradigm is predicated on women seeking help. In reality, most women with OAB adapt their lives to their symptoms rather than seek medical advice and treatment for reasons mentioned earlier like embarrassment, shame, and the incorrect assumption that it is a natural effect of aging that has to be accepted. Research has shown that women wait an average of 6.5 years before seeking treatment, and many never seek treatment at all (Gallup OAB Study 2011).

3.4 Current Treatment/Diagnostic Practices

Formal practice guidelines in the United States were established this year by the American Urological Association (AUA). According to these guidelines, a formal medical diagnosis of OAB is based upon exclusion of underlying diseases like urinary tract infections (UTIs), abnormal bladder pathology including bladder cancer (BC), diabetes (DM), and pregnancy where some of the symptoms may overlap

those of OAB. Men presenting with urinary frequency should have a prostate exam to exclude underlying prostatic disease.

In the clinician's office, OAB generally presents in one of three ways (Association of Reproductive Health Professionals 2011), with the first two ways being far more prevalent than the third:

- The patient states "I have OAB" because she is familiar with the term from advertising, friends or other HCPs.
- The patient offers a complaint of a lower urinary tract symptom (LUTS) that the healthcare provider interprets to be OAB.
- Upon proactive querying by the HCP, the patient admits to OAB symptoms.

The evaluation of the patient with OAB should focus on medical history, physical examination, and a limited laboratory evaluation. The history may be the most important component in the evaluation of the OAB patient, and the symptoms of urgency, frequency, nocturia and potential urinary incontinence are paramount. Screening for OAB requires minimal time from a healthcare provider, and a self-administered questionnaire or screener can be used in most clinical settings (Newman 2005), however, this is not the norm today.

Even after a clinical diagnosis, it is important to remember that OAB is not a disease; it is a symptom complex that is generally a benign condition. After assessment has been performed to exclude conditions requiring possible treatment or counseling, options include behavioral therapies, pharmacological therapies, a combination of the two, or even no therapy at all; depending on how severe the impact on quality of life is to the individual patient (AUA 2012).

Behavioral therapy could include pelvic floor muscle exercises, bladder re-training, urge-suppression techniques, or encouraging exercise, weight loss and/or caffeine restriction. Patients practicing behavioral therapy recorded a 57% reduction in urinary accidents, and this increased to 89% when pharmacological therapy was also incorporated (Burgio 2000).

There are currently seven FDA-approved drugs for OAB. All primarily produce anticholinergic relaxation of the detrusor muscle and all are generally of similar efficacy. Anticholinergic side effects including dry mouth, constipation, blurred vision and increased heart rate are common in the oral products, particularly in the immediate-release formulations. Lack of tolerability to these side effects often leads to poor compliance or adherence, offsetting the benefits these products can provide. In rare cases, OAB symptoms which are unresponsive to pharmacologic treatment may require more invasive treatments such as botulinum toxin injections into the bladder or bladder surgical augmentation.

It is apparent that self-management is often the norm and that women may rely on these behaviors for years as their quality of life continues to diminish. If they do learn of treatment options and seek medical advice, they may have other conditions ruled out, but may not feel that they receive satisfactory attention or meaningful and sustainable therapeutic options.

4.0 OVERVIEW OF OXYTROL DRUG PRODUCT AND PHARMACOLOGY

4.1 The Transdermal Patch System

Oxybutynin TDS is a skin patch that provides transdermal delivery of oxybutynin, the same ingredient as in Ditropan which was originally approved by the FDA in 1975. Oxybutynin TDS was approved by the FDA as a prescription product on February 26, 2003.

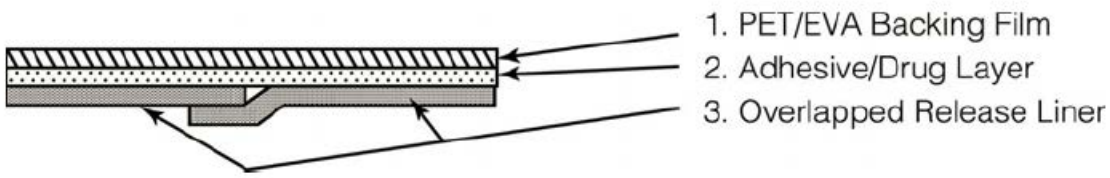
Oxybutynin TDS was developed by Watson Laboratories to address the commonly seen anticholinergic side effects that are associated with the oral antimuscarinic products. Oxybutynin TDS has advantages over oral drug administration, including improved pharmacokinetics, enhanced adherence, and a lower incidence of anticholinergic side effects (MacDiarmid 2009).

Oxybutynin TDS is a matrix-type system designed to deliver oxybutynin continuously and consistently over a 3- to 4- day interval after application to intact skin. Layer 1 (backing film) is a thin, flexible polyester/ethylene-vinyl acetate film that provides occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 (Adhesive/Drug Layer) is a case film of acrylic adhesive containing oxybutynin and triacetin, USP. Triacetin is included to increase skin permeation. Layer 3 (Release Liner) is two overlapped siliconized polyester strips that are peeled off and discarded by the patient (Figure 2).

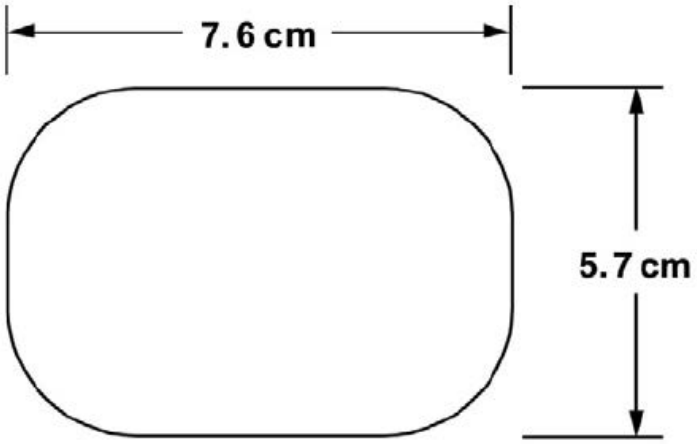
The proposed Oxytrol OTC transdermal system is identical to the current prescription product, a 39 cm^2 patch containing 36 mg of oxybutynin delivering 3.9 mg/day over a 4-day period. Individual patches will be packed in child-resistant heat-sealed pouches and will be available in a variety of retail counts.

Figure 2 Side and Top Views of Oxytrol System

Side view (not to scale)



Top view



4.2 Pharmacology

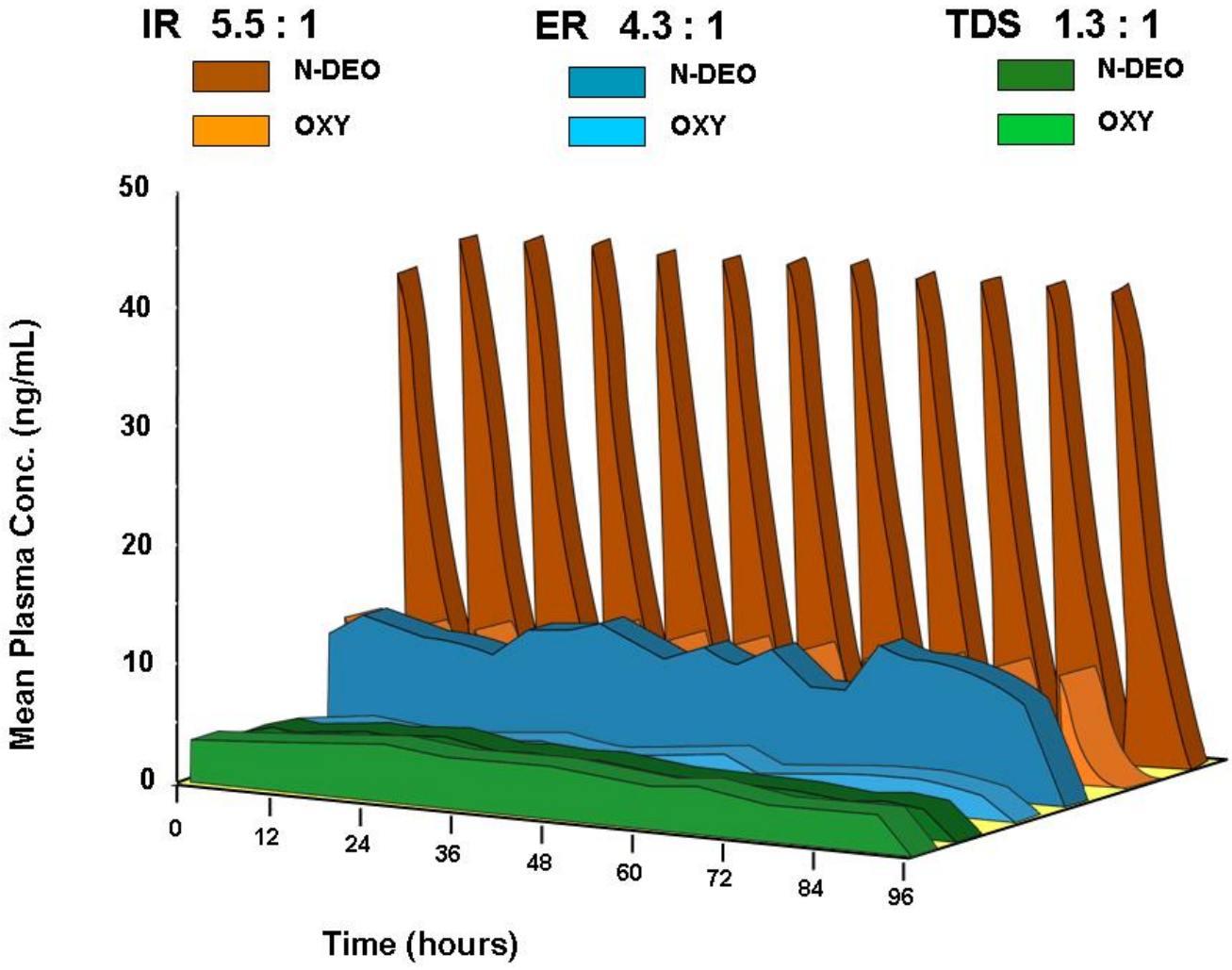
Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly in the R-isomer. The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies. 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 decreases urinary urgency and frequency of both incontinence episodes and voluntary urination (NDA 21-351).

Following systemic absorption, oxybutynin is widely distributed in body tissues and metabolized by cytochrome P450 enzyme systems, particularly CYP3A4. Less than 0.1% of the administered dose is excreted unchanged in the urine. Metabolites include pharmacologically inactive phenylcyclohexylglycolic acid and pharmacologically active N-desethyloxybutynin (N-DEO). Less than 0.1% of the administered dose is excreted as the metabolite N-DEO.

Following oral administration of oxybutynin, pre-systemic first-pass metabolism results in an oral bioavailability of approximately 6% and higher plasma concentration of the N-DEO metabolite compared to oxybutynin. The plasma concentration AUC ratio of N-DEO metabolite to parent compound following a single 5 mg oral dose of oxybutynin chloride was 5.5 compared to 1.0 for oxybutynin TDS (Figure 3). Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism, reducing the formation of the N-DEO metabolite (NDA 21-351). Only small amounts of CYP3A4 are found in skin, limiting pre-systemic metabolism during transdermal absorption.

The ratio of Cmax following immediate release oral dosing compared to that following skin application is least 10 fold greater. Since N-DEO is associated with anticholinergic side effects, this feature of transdermal administration that circumvents first-pass metabolism leads to an improved tolerability profile, in addition to smoother and more sustained plasma levels over a 3 to 4 day period.

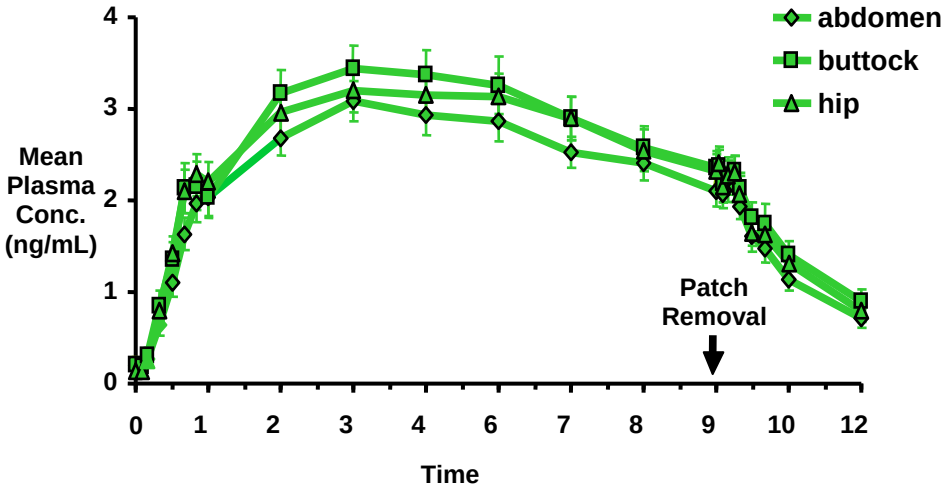
Figure 3 Plasma Concentration by Time for Immediate Release* (IR), Extended Release (ER) and Transdermal (TDS) Oxybutynin



*Extrapolated concentrations from a single OXY-IR dose = 5 mg/day; Data on File, Watson Pharma, Inc. Appell RA, et al. Mayo Clin Proc. 2003:78:696-702.)

Similar plasma concentration profiles have been shown when applied to the abdomen, buttocks, or hip, enabling the patient to rotate sites and reduce potential topical irritation. (Figure 4). Oxybutynin plasma concentration increases for approximately 24 to 48 hours reaching average maximum concentrations of 3 to 4 mg/mL, following the first application of the oxybutynin TDS 3.9 mg/day. Thereafter, steady-state plasma concentrations are maintained for approximately 96 hours, eliminating the peaks and troughs associated with oral oxybutynin.

Figure 4 Average Plasma Concentrations by Site of Administration for Single Application



In summary, oxybutynin acts as competitive antagonists of acetylcholine at postganglionic muscarinic receptors producing relaxation of bladder smooth muscle. The oxybutynin TDS is designed to provide advantages over oral products including:

- delivering a consistent concentration of oxybutynin and active metabolite throughout the 96-hour dosing interval from multiple dermal sites
- avoiding first-pass metabolism which substantially reduces the maximal parent and active metabolite concentrations compared to oral forms of oxybutynin
- an improved anticholinergic side effect profile with a low incidence of mild to moderate skin irritation

5.0 REVIEW OF CLINICAL BENEFITS (EFFICACY AND QOL) AND SAFETY

5.1 Efficacy

The prescription clinical development program to support prescription use of oxybutynin TDS included two placebos-controlled randomized Phase 3 studies (Table 1) which were reviewed as part of the original NDA, approved by the FDA in 2003. The results are summarized here.

The two Phase 3 study populations were similar in sex distribution, age, race, and duration of OAB symptoms with 49% of patients were aged 65 years or more and 92.3% female. Patients enrolled had a diagnosis of OAB based on a history of urge incontinence, urgency and frequency, with or without evidence of a neurogenic cause. Patients had no reversible causes of urge incontinence (e.g., urinary tract infection or use of diuretics) and no evidence of overflow incontinence. One of the two Phase 3 studies (O99009) enrolled 80% of patients who were naïve to prior pharmacologic treatment for incontinence while study O00011 enrolled subjects with a prior l response to an anticholinergic. In both of these studies each treatment arm, including placebo, also received additional lifestyle and behavior instructions. Lifestyle and behavioral modification has been demonstrated to improve OAB symptoms in the absence of pharmacologic intervention.

Table 1 Topline Characteristics of Clinical Efficacy Studies

Study	Phase	Design	Objective	Duration/Sample Size	Primary Endpoint
Study O99009	3	Multicenter, open label, placebo controlled	Safety & efficacy Compared three sizes (13, 26 and 39 cm^2) of Oxybutynin TDS with placebo TDS.	12 weeks Oxybutynin = 388 13 cm2 (130); 26 cm2 (133), 39 cm2 (125) Placebo = 132 Open label extension = 411	Change in number of episodes of incontinence per week over treatment period compared to placebo
Study O00011	3	Multicenter, double blind	Safety & efficacy Oxybutynin TDS (39 cm^2; 3.9 mg/day) versus placebo and with 4 mg tolterodine long-acting capsules	12 weeks Oxybutynin = 121 Tolterodine = 123 Placebo = 117 Open label extension = 284	Change in mean urinary incontinence episodes during treatment period
(Source: from CSRs of Studies O96017, O99009 and O00011, NDA 21-351)					

5.1.1 Study O99009 (Phase 3) Efficacy Results

The primary objective of the double-blind period of this study was to compare the safety and efficacy of three doses (13, 26 and 39 cm^2) of oxybutynin TDS with placebo during 12 weeks of treatment. All patients began a 2-week washout from their current treatment or began a disease stabilization period. During this washout period, all patients were instructed to: 1) maintain a consistent level of usual fluid intake, and 2) maintain his/her usual program of non-pharmacological management of incontinence (e.g., pelvic floor exercise, timed voiding/bladder training). This practice was continued throughout the entire study.

The primary efficacy endpoint was the change from baseline to endpoint in the number of incontinence episodes recorded in the urinary diary comparing the active patch group with the placebo patch group during the double blind period. The secondary objectives included comparisons of daily urinary frequency, urinary volume per void, quality of life (QoL) scores (for the Incontinence Impact Questionnaire (IIQ), and the Urogenital Distress Inventory (UDI), as well as safety assessments. The IIQ questionnaire measures the psychosocial impact of urinary incontinence in women and the UDI questionnaire assesses the degree to which symptoms associated with incontinence are troubling. The QoL results are summarized in Section 5.2 and the details of individual tool results are included in Appendix 2. The primary and secondary parameters were analyzed by an analysis of covariance.

In the double-blind period, patients treated with the 39 cm^2 oxybutynin TDS experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint compared with placebo (the primary endpoint). The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week, or nearly 3 episodes per day, compared with the median decrease of 15 episodes per week in the placebo group.

Statistically significant improvements were also observed in the average daily urinary frequency (median decrease of 2 episodes per day) and the average urinary volume per void (median increase of 24 mL per void) in the 39 cm^2 group compared with placebo. The comparative data from placebo and from the 39 cm^2 study group for the primary and secondary objectives are shown in Table 2.

In the double-blind period, patients treated with the 39 cm^2 oxybutynin TDS experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint compared with placebo (the primary endpoint). The median number of incontinence episodes in the 39 cm^2 group decreased by 19 (61.3%) episodes per week (from 31 to 12), or nearly 3 episodes per day, compared with the median decrease of 15 episodes per week in the placebo group.

Statistically significant improvements were also observed in the average daily urinary frequency (median decrease of 2 episodes per day) and the average urinary volume per void (median increase of 24 mL per void) in the 39 cm^2 group compared with placebo. The comparative data from placebo and from the 39cm^2 study group for the primary and secondary objectives are shown in Table 2.

Table 2 Summary of primary and secondary efficacy endpoints; placebo vs. oxybutynin TDS 39 cm^2 study groups; double-blind period for Phase 3 study 099009

Parameter	Placebo (N=127) Median	OXYTROL TDS 3.9 mg/day (N=120) Median
Reduction in Weekly Incontinence Episodes (Primary Objective)		
Baseline	30	31
At 12 wks. (Change, %)	15 (-15, -50%)	12 (-19, -61%)
p value vs. placebo	0.0265*	
Reduction in Daily Urinary Frequency (Secondary Objective)		
Baseline	11	11
At 12 wks. (Change, %)	10 (-1, -9%)	9 (-2, -18%)
p value vs. Placebo	0.0313*	
Increase in Urinary Volume per Void (mL) (Secondary Objective)		
Baseline	166.5	168
At 12 wks. (Change, %)	172 mL (+5.5, +3%)	194 mL (+26, +15%)
p value vs. placebo	0.0009*	

*Comparison significant if p ≤ 0.05. Source: CSR of Study O99009, NDA 21-351

5.1.2 Study O00011 (Phase 3)

This Phase 3 study was a multi-center, randomized, double-blind, double-dummy, placebo-controlled study comparing oxybutynin TDS (39cm^2) versus tolterodine long-acting capsules (4 mg oral) in patients with overactive bladder.

The primary objective of the study was to compare the safety and efficacy of transdermal oxybutynin versus active (4 mg tolterodine long acting capsules) and placebo in OAB patients who had previously achieved a beneficial response from anticholinergic treatment. The primary efficacy endpoint was the change from baseline to end of treatment (week 12) in average number of urinary incontinence episodes per day as recorded in the urinary diary.

Secondary endpoints included: change from baseline in average daily urinary frequency and average urinary volume per void and two QoL instruments: the IIQ and the UDI. IIQ questionnaire measures the psychosocial impact of urinary incontinence in women and UDI questionnaire assess the degree to which symptoms associated with incontinence are troubling. The QoL impact is summarized in Section 5.2 and the details of individual tool results are included in Appendix 2.

Patients were primarily Caucasian women with a prior history of OAB. Patient age ranged from 18 to 89 years with an average age of 63 years. Patients who met the eligibility criteria received one of three randomized treatments: 39 cm^2 oxybutynin TDS (3.9 mg/day), 4 mg tolterodine long acting capsules, or placebo treatment. Information on bladder function and behaviors that may contribute to incontinence

and instructions on bladder control and fluid management techniques were provided to all patients at screening.

Fluid management techniques were provided to all patients at screening.

Oxybutynin TDS treatment resulted in a significant decrease in urinary incontinence episodes from baseline to endpoint compared with placebo (p = 0.0137). Median daily incontinence episodes decreased by 3 episodes per day for Oxybutynin TDS, compared with a decrease of 2 episodes per day in the placebo group. Oxybutynin TDS and tolterodine were comparably effective, both treatments decreasing episodes by 3 episodes per day.

Daily urinary frequency decreased by a median of 2 micturitions/day during Oxybutynin TDS treatment (p = 0.1010). Improvement was statistically significant compared with placebo (p = 0.0036). Average urinary void volume median increase was 24 mL during Oxybutynin treatment (p = 0.0010). The individual data points are shown in Table 3.

Table 3 Summary of primary and secondary efficacy endpoints; placebo vs. Oxybutynin TDS 39 cm^2 and Tolterodine study groups; double-blind period for Phase 3 study O00011

Parameter	Placebo (N=117) Median	OXYTROL 3.9 mg/day (N=121) Median	Tolterodine (N=123) Median
Daily Incontinence Episodes(Primary Objective)			
Baseline	4	4	4
At 12 wks. (Change, %)	2 (-2, -50%)	1 (-3, -75%)	1 (-3, -75%)
p value vs. placebo	NA	0.0137*	0.0011*
Daily Urinary Frequency (Secondary Objective)			
Baseline	12	12	12
At 12 wks. (Change, %)	11 (-1, -8%)	10 (-2, -16%)	10 (-2, -16%)
p value vs. Placebo	NA	0.101	0.0025*
Urinary Void Volume (mL) (Secondary Objective)			
Baseline	171	160	165
At 12 wks. (Change, %)	176.5 (+5.5, +3.2%)	184 (+24, 15%)	194 (+29, 18%)
p value vs. placebo	NA	0.0010*	0.0017*

*Comparison significant if $p \leq 0.05$. Source: CSR of Study O00011, NDA 21-351

Achievement of full continence was not a pre-specified endpoint for the study; however, for individual patients this is a very important treatment outcome. Almost twice as many patients who received active treatment achieved complete continence when compared with patients who received placebo. As shown in Table 4 below, n = 47 (38.8%) patients treated with Oxybutynin TDS achieved full continence at their last study evaluation at week 12. The bladder training and behavioral modification aspects of the study may have contributed to the relatively high placebo response.

Table 4 Patients achieving full continence at endpoint in Phase 3 study O00011

	Patients Achieving Full Continence at 12 weeks of Treatment	
Treatment Group (N)	**n**	**%**
Oxybutynin TDS (n=121)	47	38.8% (47/121)
Tolterodine (n=123)	47	38.2% (47/123)
Placebo (n=117)	26	22.2% (26/117)

(Source: CSR of Study O00011, NDA 21-351, listing 16.2.7.1.3, double-blind period)

5.1.3 Responder Analyses

A post-hoc responder analysis was performed using both Phase 3 trials (study O99009 and O00011). Responders were defined by using clinically meaningful measures for the primary endpoint and two key secondary endpoints at week 12.

- Urinary incontinence: 100% and 50% decrease in incontinence episodes from baseline (discussed within this section)
- Urinary frequency: 10% , 20% or 30% reduction in urinary frequency from baseline (see Appendix 1)
- Urinary volume: 10% , 20% or 30% increase in urinary volume from baseline (see Appendix 1)

Subgroup analyses were performed for gender and age. For the male responders the sample size was too small for statistical interpretation. Age groups were grouped as either under 65 or 65 years and over. All of the responder analyses were performed separately for each gender and age group. The statistical method is described in Appendix 1.

For all patients and for all females, at 12 weeks of treatment the oxybutynin TDS group compared to placebo showed statistically significant reduction in urinary incontinence episodes. (Table 5) In all patients, full continence was achieved in 62 (25.9% of N) of the oxybutynin TDS responders compared to 37 (15.2% of N) in the placebo group (P = 0.0039). In all female subjects, full continence was achieved in 51 (23.4% of N) of the responders in the oxybutynin TDS group compared 31(13.8% of N) in the placebo group (P = 0.0098).

Table 5 Results of responder analysis for all patients and all female subjects (Pooled data from Phase 3 studies O99009 and O00011)

All patients		Placebo			Oxybutynin TDS			
		N	R	% R	N	R	% R	P*
All Patients								
Urinary Incontinence Episodes	A. 100 % reduction	243	37	15.2%	239	62	25.9%	0.0039
Urinary Incontinence Episodes	B. 50 % reduction	243	142	58.4%	239	175	73.2%	0.0006
All Female Subjects								
Urinary Incontinence Episodes	A. 100 % reduction	225	31	13.8%	218	51	23.4%	0.0098
Urinary Incontinence Episodes	B. 50 % reduction	225	129	57.3%	218	156	71.6%	0.0018

Notes: R = Responders, %R = %Responders, *Comparison significant if $p \leq 0.05$

The goal of this post-hoc responder analysis was to better understand if a treatment effect was clinically meaningful. A limitation of this responder analysis is reduced power in comparison to the original analysis.

Overall for all patient population and the female population, the treatment effect in the oxybutynin TDS study group compared to placebo was statistically significant and clinically meaningful for improvement in urinary incontinence, urinary frequency and urinary volume per void following 12 weeks of treatment.

5.1.4 Efficacy Conclusions from Phase 3

The Original Phase 3 clinical development program included two placebo controlled randomized studies, both of which showed statistical superiority of oxybutynin TDS over placebo. The effect size was moderate and consistent with a positive control oral product (tolterodine). It is important to recognize that all of the patients in both studies received information on bladder function and behavior modification with instructions on bladder control and fluid management techniques. This likely contributed to the placebo response.

Both Phase 3 studies met the primary endpoint showing significant reduction in the incidence of incontinence episodes at week 6 and week 12 for oxybutynin TDS versus placebo. Incontinence is usually considered as one of the most bothersome symptoms of OAB. About 39% of the patients in study O00011 achieved full continence at the end of study compared to 22% for placebo. Efficacy for oxybutynin TDS was also demonstrated for the secondary endpoints in both Phase 3 studies, demonstrating significant reductions in urinary frequency and significant increase in void volume. The post hoc responder analysis quantified similar trends. The impact of urinary symptoms varies according to each patient's priorities and lifestyle. For example, urgency may have greater impact on a professional who travels than it does on a retired person. A better understanding of the overall benefits of OAB treatment can be obtained from use of validated instruments to assess QoL and

relate improvements in QoL to changes in OAB symptoms. These aspects are examined in the next section.

5.2 Quality of Life (QoL) Assessments

OAB has a profound impact on QoL. OAB impacts many aspects of daily living, resulting in a progressive decline in emotional well-being, productivity at home and at work, social relationships, sexual intimacy, and physical functioning. Treatment-related improvements in objective outcomes may not reflect subjective improvements in symptoms or other aspects of the condition that matter most to the patient (Khullar 2006). For example, patients may perceive a greater benefit from fewer incontinence episodes or a reduction in the amount of leakage, regardless of the number of episodes (Donovan 2002).

Clinical efficacy data collected to date demonstrate that oxybutynin TDS significantly improves urinary incontinence episodes, urinary frequency, and urinary void volume. Instruments that measure patient's quality of life (QoL) provide additional information of how the clinical improvements are meaningful to the patient. This section summarizes QoL data collected from the two Phase 3 studies and one Phase 4 study aimed specifically at QoL measures.

The QoL data is presented in detail in Appendix 2 from the two Phase 3 controlled studies (O99009 and O00011) and one large, open-label, naturalistic Phase 4 study (MATRIX) which evaluated the QoL impact of Oxytrol TDS on patients with OAB. The MATRIX study was not placebo controlled , however more than 2800 patients (N=2878) were enrolled to ensure that each of the 3 QoL assessments would have at least 467 completers to detect a 3% changes from baseline, with 90% of power (1-β) and a significance level (α) of 0.05.

5.2.1 QoL Data from Phase 3 Studies

Both Phase 3 trials (study O99009 and O00011) evaluated QoL using the IIQ and the UDI. These studies including the QoL data results were reviewed as part of the original prescription NDA approved in 2003.

In study O99009, the IIQ total scores showed a significant positive effect of oxybutynin TDS treatment compared to placebo. In the oxybutynin TDS treatment group at EOT, mean IIQ total score decreased approximately 39% compared to 28% for placebo ($p = 0.0327$). Similar improvements were also seen in the following subscales: physical activity (ability to do household chores, shopping, recreation) ($p = 0.0472$); ability to travel ($p = 0.0115$); and emotional health ($p = 0.0480$). The decrease in total UDI score for females was statistically significant for oxybutynin TDS compared to placebo ($p = 0.0266$),

In study O00011, patient QoL was improved during Oxybutynin treatment for total IIQ score ($p = 0.0271$) and trends in UDI. Individual IIQ subscales (travel, social

relationships, emotional health, and physical activity) improved in general, but the magnitude of change was significant only for the improved ability for travel (p = 0.0018). For Oxytrol, the magnitude of UDI score change was significant (p = 0.0156) compared to placebo for irritative symptoms.

5.2.2 QoL in the MATRIX Phase 4 Study

The effects of oxybutynin TDS on QoL in OAB patients was evaluated in a Phase 4 study titled MATRIX, which was a naturalistic open-label study. Adult subjects with OAB were treated with oxybutynin TDS for up to 6 months and QoL was assessed at baseline, at Month 3, and at Month 6 using 3 validated questionnaires:

- King's Health Questionnaire (KHQ) for the assessment of health-related QoL
- Beck Depression Inventory (BDI) for the evaluation of the existence and severity of symptoms associated with depression
- Work Productivity Questionnaire (WPQ) for the estimation of work activity impairment and productivity loss.

Following the oxybutynin TDS treatment, significant KHQ score reductions were observed in all 10 KHQ domains, at both Month 3 and Month 6 (all $p < 0.0001$). A change from baseline of at least 5 points on KHQ domains indicates a change that is meaningful to patients and is indicative of a clinically meaningful improvement in health-related quality of life after treatment. (Kelleher 2004) Except for General Health Perceptions, the score reductions of all the other 9 domains were considered clinically meaningful.

The BDI cumulative scores in patients treated with oxybutynin TDS were 10.7±9.51 (N=2581, Median 8.0) at baseline, 8.5±8.7 (N=1668, Median 6.0) at Month 3, and 7.4±7.76 (N=1379, Median 5.3) at Month 6, respectively. Decreases in BDI scores indicate an improvement from depression. The BDI score reductions at Month 3 and Month 6 were -2.0±6.62 and -2.8±7.08, respectively; both were statistically significant ($p < 0.0001$).

Lastly, significant WPQ score reductions were observed in all 4 work limitation scales ($p \leq 0.002$), the total WPQ Index ($p < 0.0001$) and Productivity Loss ($p < 0.0001$), at both Month 3 and Month 6. The mean Productivity Loss at baseline, Month 3, and EOS in Month 6 were 7.7%, 5.5%, and 4.8%, respectively, with the mean changes from baseline of -2.2% and -2.9%. For a full-time employee who works 40 hours per week, a reduction in Productivity Loss of 2.9% is equivalent to a gain of ~ 60 hours/year, a little more than one working week per year.

At baseline, 43% of patients reported that they could not enjoy things as much as they used to; 46% had worse concentration difficulty; 52% became less interested in sex or completely lost interest; 68% got tired or fatigued more easily and 71% of patients reported having less energy. All were attributed to the associated bladder

problem. At the end of the oxybutynin TDS treatment, the percent of patients having the above-listed issues dropped to 33%, 34%, 39%, 53%, and 63%, respectively (all $p < 0.0001$).

5.2.3 QoL Conclusions

- Important QoL impact was noted in both placebo controlled Phase 3 studies as well as the large open label Phase 4 study.
- Both the Phase 3 and Phase 4 data demonstrated statistically significant QoL benefits for patients suffering from OAB.

5.3 Review of Clinical Safety

5.3.1 Safety Data from Controlled Studies

Across the Phase 2 and 3 studies, 663 subjects reported 1,867 AEs, the majority of which were mild or moderate in severity. In the pooled Phase 3 database, the overall incidence of AEs was greater in patients who received oxybutynin TDS (73.0%) compared to placebo TDS (56.6%).

Overall, 13.0% of patients discontinued active transdermal oxybutynin treatment due to adverse events. 6.8% discontinued due to application site reaction. Discontinuation for dry mouth was slightly greater in the oxybutynin TDS group (0.7%) than placebo (0.4 %). Dry mouth is considered as a classic anticholinergic side effect, is self-recognizable and is reversible following drug discontinuation.

Application site AEs occurred in 23.1% of all patients treated with active oxybutynin TDS. Pruritus was the most common application site reaction at all oxybutynin dose levels and occurred in 14.5% of patients receiving active oxybutynin treatment. In controlled studies of < 6 weeks duration, 13.0% of active TDS patients experienced application site AEs (including 6.8% who discontinued due to skin reaction) compared with 5.6% of placebo TDS patients.

In controlled Phase 3 studies of 0-12 week's duration, application site reactions were most commonly reported, see Table 6. In majority of the cases the application site AEs was considered to be of mild or moderate in intensity. The incidence rate of severe application site AEs (blisters, severe redness) tended to be highest in the 39 cm^2 dose group. The incidence increased from 1.8% for the 13 cm^2 to 4.8% for 39 cm^2oxybutynin TDS treatment group. In the placebo TDS group, two patients experienced a severe application site AE.

The majority of systemic AEs were consistent with the known anticholinergic side effects of oxybutynin. However, the frequencies of these AEs were low and often close to the occurrence in placebo-treated patients, and substantially lower than the incidences seen with oral anticholinergic dosing. The most commonly reported anticholinergic AE was dry mouth. Other anticholinergic AEs included constipation, dizziness, nausea, somnolence, abnormal vision, dysuria and palpitations (Table 6).

In controlled studies, dry mouth occurred with approximately equal frequency in the active and placebo TDS groups and with much lower frequency than in patients receiving oral oxybutynin. In patients treated in controlled studies < 6 weeks, dry mouth occurred in 6.8% of active TDS patients compared with 4.4% of placebo TDS patients. Approximately 58% of patients treated with oral oxybutynin reported dry mouth. In controlled studies 0-12 weeks, 7.5% of active TDS patients compared with 5.2% of placebo TDS patients experienced dry mouth (Table 6). The incidence of dry mouth was < 10% in each of the TDS dose groups in both controlled and uncontrolled studies.

There was no apparent relationship between the overall incidences of application site AEs or the severity of application site AEs over time. In patients receiving active TDS between 0-6 weeks, 11.5% reported application site AEs, 11.2% at 6-12 weeks duration, 11.2% at 12-24 weeks duration, and 6.3% at > 24 weeks duration. This low rate of application site AEs with longer duration could be explained by the possible bias by discontinuation. In the OTC environment a consumer could possibly and similarly simply discontinue when experiencing any intolerable application site reaction. The proportion of patients that reported mild, moderate, or severe application site AEs was essentially the same between the 0-6, 6- 12,12-24, and > 24 week duration of exposure : 5.4%, 4.1%, and 3.6% for 0-6 weeks, 4.6%, 5.5%, and 2.0% for 6-12 weeks, 3.4%, 5.4%, and 2.0% for 12-24 weeks, and 2.8%, 2.1%, and 2.1% for > 24 weeks of active treatment for mild, moderate, and severe application site AEs, respectively. Thus there was no evidence that chronic use was associated with worsening of application site reactions.

Table 6 Summary of all treatment-emergent adverse events (>2.0%) by preferred term and treatment in OAB patients

	All Placebo (n=249)	All Oxybutynin TDS (n=547)	All Oral Oxybutynin (n=38)*
Mean exposure (days)	**69.7**	**70.5**	**42.7**
Patients with AEs (%)	**141 (56.6%)**	**338 (61.8%)**	**30 (78.9%)**
Drug- related AEs (%)	**61 (24.5%)**	**219 (40.0%)**	**30 (78.9%)**
Preferred Term, Classic ACH AEs			
Constipation	7 (2.8)	19 (3.5)	10 (26.3)
Dry Mouth	13 (5.2)	41 (7.5)	22 (57.9)
Nausea	8 (3.2)	18 (3.3)	7 (18.4)
Dizziness	6 (2.4)	15 (2.7)	6 (15.8)
Preferred Term, Skin Related AEs			
App. Site Pruritus	13 (5.2)	74 (13.5)	0 (0.0)
App. Site Erythema	6 (2.4)	28 (5.1)	0 (0.0)
Preferred Term, Other AEs			
Diarrhea	14 (5.6)	25 (4.6)	1 (2.6)
Headache	7 (2.8)	20 (3.7)	2 (5.3)
Inflicted Injury	7 (2.8)	21 (3.8)	0 (0.0)
Myalgia	2 (0.8)	15 (2.7)	0 (0.0)
Rhinitis	9 (3.6)	21 (3.8)	1 (2.6)
Sinusitis	4 (1.6)	17 (3.1)	0 (0.0)
Urinary Tract Infection	11 (4.4)	17 (3.1)	2 (5.3)
Back Pain	8 (3.2)	15 (2.7)	0 (0.0)

*from the Phase 2 study
Source: Table 8.3.1, ISS, NDA 21-351(Studies included: O96017, O99009, and O00011, 0-12 weeks. Treatment only, >2.0% AEs in all oxybutynin TDS)

Across all arms of the Phase 2 and 3 studies there were no deaths and 37 subjects reported 47 serious adverse events (SAEs) (Appendix 3) across. Most SAEs were of short duration and resolved without sequelae prior to discharge from the study and none of the SAEs were attributed to the study drug. As a result of the SAEs, 9 patients discontinued early. The remaining 28 patients completed the study according to the dosing regimen. Of the 9 patients who discontinued, 2 patients (one each in the 26 cm^2 and placebo groups) suffered moderate chest pain, 1 patient in the 13 cm^2 group had a syncope episode, 1 patient in the 13 cm^2 group had severe episodes of pneumonia/dyspnea as well as severe sepsis, and 1 patient in the 39 cm^2 group experienced severe pancreatitis in the controlled period of Study O99009. Two patients discontinued from the uncontrolled period of Study O99009, 1 patient in the 13 cm^2 group due to moderate chest pain and 1 patient in the 26 cm^2 group after being diagnosed with a severe malignant mixed Müllerian tumor which resulted in death 2 months after discontinuation. Of the other 2 patients discontinued during the controlled period of Study O00011, 1 patient in the 39 cm^2 treatment group had a syncope episode and bradycardia which were resolved and 1 patient in the 39 cm^2 group had severe back pain which also resolved. There were no trends in SAE incidences across different treatment groups.

5.3.2 MATRIX (Phase 4 Study)

This study was a Phase 4 study conducted by Watson Laboratories between May 2004 and May 2005. The safety population from the MATRIX study includes 2,881 adult OAB patients all of whom received Oxytrol. The study population was predominantly female (87.1%), and skewed towards older subjects, with a median age of 63 years. For patients < 65 years of age (n = 1510), median age was 52 years, and median age was 75 years for those ≥ 65 years of age.

The patients enrolled in the MATRIX trial had many co-morbid medical conditions stratified by age (under 65 years and 65 years and older). Co-morbid medical conditions occurring in greater than 50% of the total population were cardiovascular (55.4%), musculoskeletal (54.7%), or unspecified (other) conditions (55.4%). The older cohort had a greater incidence of cardiovascular (70.0% versus 55.4%), musculoskeletal (62.9% versus 54.7%), endocrine (42.4% versus 36%), and hematological/lymphatic (9.9% versus 8.8%) disorders. Use of multiple concomitant medications was common. Commonly reported concomitant medications included statins, antidepressants, sex hormones, analgesics, PPIs, antiplatelet drugs, antidiabetic drugs, diuretics, psycholeptic drugs, NSAIDs, COX-2 inhibitors, and antihistamines. Of the 2,881 subjects randomized to treatment, 1,409 (48.9%) completed 6 months of treatment.

Overall 1,328 patients in the MATRIX trial reported a total of 2,834 AEs. A total of 864 patients reported 1,439 AEs (50.8% of all AEs) which were considered at least potentially related to oxybutynin TDS treatment. 105 patients reported 168 serious AEs. Of these, only 1 event, a urinary tract infection in a 57 year old woman was considered possibly related to oxybutynin TDS treatment. Appendix 4 lists adverse events by System Organ Class (SOC) in descending order of frequency for those SOC's accounting for at least 1% of all reported AEs. The SOCs with the most AEs are General Disorders & Administration Site Conditions (732 AEs) and Skin & Subcutaneous Tissue Disorders (397 AEs), which together account for almost 40% of all AEs. This trend was similar to that observed with the Phase 3 trials.

5.3.3 Post-Marketing Safety Data

Post marketing safety surveillance data has been obtained and summarized from a variety of sources reporting spontaneous adverse events.

5.3.3.1 US Postmarketing Experience

US Post-marketing safety data have been reviewed for adverse events associated with use of various oral and transdermal dose forms of oxybutynin from 2003 through the end of December 2010. Since oxybutynin TDS approval, 28 million Oxytrol patches have been sold in the US with an estimated 270,000 person-years of experience. Since its launch, 9,690 AEs associated with use of oxybutynin TDS in the US have been reported to the FDA in periodic update reports. Almost two-thirds (6,435 events, 66.4%) are considered non-serious listed (already included in labeling) AEs, and represent events that may be expected based on the drug properties and product label warnings. Another 30.2% (3,021 AEs) are other non-serious events. A total of 244 serious AEs have been reported in association with use of Oxytrol. These represent approximately 2.5% of all AEs. The AE reports for oxybutynin TDS have not resulted in label changes, with the exception of dizziness in 2006. A warning about angioedema, which has been reported with oral oxybutynin use, was added to the label in 2011.

The post-marketing safety trends of oxybutynin TDS are consistent among clinical trials and marketed prescription use. The most frequently reported adverse events associated with the use of this product relate to mild to moderate reversible administration site irritation. The leading system organ class for AE reports is General Disorders and Administration Site Conditions, accounting for over half of all total AEs (5,474 AEs; 56.5%). The most frequent events in this category were application site erythema, application site pruritus, and drug ineffective, with 1,416, 1,053, and 960 AEs, respectively. These 3 events account for 35.4% of all reported AEs since product launch. Besides application site related AEs and lack of effectiveness, fatigue, with 95 reported AEs (0.98% of all AEs) was a relatively frequent complaint. Gastrointestinal disorders (1,111 AEs) accounted for 11.5% of all reported AEs. The most frequent event in this organ class was dry mouth with 304 AEs representing 3.14% of all reported AEs and 27.4% of AEs for this organ class. Dry mouth likely reflects the anticholinergic action of oxybutynin and was the major anticholinergic-related AE associated with the use of oxybutynin TDS. Other frequently reported gastrointestinal disorders are nausea and vomiting, constipation, and diarrhea, with 170, 161, and 105 events, respectively. The other AEs which account for ≥ 1% of reported events are blurred vision (196 AEs) dizziness (186 AEs), headache (176 AEs), and somnolence (156 AEs).

5.3.3.2 Ex-US Post marketing safety data

Tabulations from the safety data submitted to European regulatory agencies list a total of 3,738 AEs reported by 1773 patients having an association with transdermal

oxybutynin including serious AEs (302 events in 91 cases, 8%). This represents an overall frequency for adverse events of approximately 95 AEs per 10,000 patient-years of treatment and 7.7 SAEs per 10,000 patient years of treatment. The most frequent AE as reported by preferred term in tabulations from all Periodic Safety Update Reports (PSURs) is “application site erythema”, with 417 events. The second most frequently reported AE in PSURs is “drug ineffective”, with 408 events. Dry mouth is the most frequently reported event related to anticholinergic activity of Oxytrol, with 99 AEs. This represents 2.6% of all reported AEs in the PSURs and an incidence of 2.5 events per 10,000 patient-years of treatment. Dizziness, blurred vision, constipation, and somnolence, have 61, 56, 51, and 51, associated AEs, respectively.

5.3.3.3 American Association of Poison Control Centers (AAPCC)

AAPCC has been reviewed for use of various oral and transdermal dose forms of oxybutynin from 2003 through end of December 2010. The AAPCC database was reviewed for the period February 1, 2003 through August 31, 2011. There were 26 cases involving Oxytrol TDS, 24 cases involving Gelnique transdermal gel, 7 cases involving oxybutynin oral tablets, and 12 cases identified as other or unidentified oxybutynin formulation. Exposures to oxybutynin products resulting in reports to the AAPCC were characterized mostly as unintentional exposures (general, misuse, or therapeutic error) or as adverse drug reactions. There was a single report with an unknown formulation of intentional misuse. This case involved the use of a total of 10 medications, from which the relative contribution of oxybutynin to the observed clinical effects (confusion and drowsiness) was ranked as 7th. Two reports of Intentional Suspected Suicide were reported to be associated with use of the oxybutynin TDS and one with use of oxybutynin transdermal gel. The relative contribution of oxybutynin to observed clinical effects in these suspected suicide cases (coma, drowsiness and meiosis with the Oxytrol patch and urinary incontinence with the Gelnique transdermal gel) was very low (8th of 8 medications, 9th of 10 medications, and 9th of 10 medication) for each case; concomitant medications were most likely of principal concern. Overall the small numbers of AEs listed at AAPCC provides interpretable safety trends data for Oxytrol.

5.3.4 Safety Experience from the CONTROL Actual Use Study

In CONTROL (see Section 6.7) Oxytrol use was monitored by interview and by subject diary. Of the 785 subjects who reported Oxytrol use in an interview, 727 also recorded use in a diary (verified users). In the 727 verified users, the median duration of Oxytrol use was 45 days. Of the 785 subjects who reported Oxytrol use by interview, 975 AEs were reported by 519 subjects with 4.5% of subjects having at least one SAE and 14.0% permanently discontinuing use of Oxytrol because of an AE with 1.7% discontinuing because of an SAE.

In general the pattern of SAEs, AEs associated with discontinuation and AEs in general were consistent with that expected in a broad general population. There were 48 SAEs reported in 35 of the subjects with one death secondary to viral pneumonia. SAEs occurring in more than one subject were UTIs (N=3), stroke (cerebrovascular accident; N=3), back pain (N=2), chest pain (N=2), and cholecystitis (N=2). All 3 events of UTI were reported by users who had stopped using Oxytrol before the SAE onset. Two of the 3 incidences of stroke were reported by subjects after stopping drug use.

Application site AEs were the most common AEs associated with discontinuation. UTIs were associated with discontinuation in 1.3% of subjects and are discussed in more detail in the next section. Overall, 5 events were classified as severe with 2 of these consistent with UTI.

Most AEs were classified as mild or moderate in intensity with 3.8% reported as severe (Appendix 5). As with AEs associated with discontinuation, the most frequent AE reported in CONTROL was application site irritation (17.2%) None of the application site AEs was classified as severe and most were classified as mild. Other potential Adverse Drug Reactions including dry eye, dry mouth, and constipation were reported at an incidence of greater than 1% but less than 5% of possible users. UTIs were reported in 6.1% of possible users.

There were 61 subjects (7.8%) who reported 66 UTIs when combining UTIs and cystitis in CONTROL (one subject had UTI and cystitis). Of the 61 subjects with UTIs, 27 were diagnosed with UTI or bladder infection while using Oxytrol based upon information reported during follow up interview. An additional 34 subjects reported UTIs or bladder infections that were collected outside of the use period of the study and were not evaluated for ongoing use behavior. With the exception of one subject who did not recognize symptoms of UTI, the subjects were either asymptomatic or developed UTI symptoms after stopping use of Oxytrol.

Three UTIs were classified as SAEs, and although they occurred in subjects who had used Oxytrol, all three subjects had stopped using Oxytrol before the diagnosis of the UTI. All 3 discontinued use of Oxytrol and did not restart treatment.

Overall, 461 subjects (443 verified users, 10 non-verified users, and 8 nonusers), had urinalysis performed at Week 12 or, for the early withdrawals, at exit. Of the 73 verified users who consulted their doctors about their urinalysis test results, 27 provided feedback at Week 12 about the doctor's diagnosis. Of the 27, 20 had been diagnosed by their physician prior to their Week 12 urinalysis with either a UTI (N=16) or a bladder infection (N=4)

There were two cases of diabetes and 2 cases of increased blood glucose measured in laboratory investigations that were reported in CONTROL. One subject was diagnosed with diabetes less than two weeks after starting Oxytrol, and discontinued after receiving the diagnosis. The other cases occurred before the

subject started using Oxytrol. There were no cases of bladder cancer. Six subjects reported 7 incidences of urinary retention. All 7 were not acute and none were classified as serious.

5.3.5 Published literature review

A literature search was conducted in the PubMed database for English-language articles published between 1996 through August 2011. Key words included the active ingredient name oxybutynin, and drug names Oxytrol, Gelnique, or Ditropan. Particular attention was paid to publications that could potentially provide safety information relative to special populations, associations with use of concomitant medications, associations with comorbidities, and risks of over dosage. Review articles were excluded. The search initially identified 220 articles. From these, 31 were selected that included safety findings of particular interest and importance. The review identified only one study reporting events associated with transdermal oxybutynin, excluding articles that summarize clinical trials submitted with NDA 21-351. All other articles referred to oral dosage forms of oxybutynin, which are associated with higher systemic levels of the drug and its active metabolite. It is well established, that there are fewer and less severe systemic adverse events related to anticholinergic effects with topical compared to oral oxybutynin. None of the information in these publications present evidence for an important new safety signal.

5.3.6 Overdose

Overdose with oral oxybutynin has been associated with anticholinergic effects including central nervous system (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 symptomatic treatment.

Based on the composition of the Oxytrol patch, the patch geometry and the solubility of the oxybutynin, the bioavailability of oxybutynin from oral ingestion of a patch would most likely be 100%. However, the rate of absorption is unknown as release studies in simulated gastric and intestinal fluids have not been performed. In post-marketing experience, there have been no oral ingestions reported. However, oral ingestion by a 5 to 15 year old child could produce toxic oxybutynin levels if 25 mg or more of the 36 mg is immediately released. This led to child resistant packaging being developed for the nonprescription Oxytrol product. There are no reports of overdose from AAPCC with Oxytrol TDS. As many as three patches have been used concurrently in small clinical studies with no adverse effects. Theoretically, it would require at least 3 patches for a person to develop plasma concentrations of

oxybutynin to approximate the levels measured after one 10 mg tablet of oral immediate release oxybutynin.

5.3.7 Safety Summary for Oxytrol

The clinical studies which supported FDA's approval of oxybutynin TDS (39 cm^2 patch providing a nominal dose of 3.9 mg/day of oxybutynin HC), demonstrate its general safety. The most frequent adverse events observed in these studies were application site related events of irritation and inflammation. These represented a combination of effects of the patch itself as well as topical application of oxybutynin. Most of these events were of mild or moderate severity, and the events resolved with removal of the patch and without sequelae. Some adverse events related to the anticholinergic mechanism of action of oxybutynin were reported. The most prevalent adverse event related to the drug's mechanism of action was dry mouth. Overall, dry mouth was the second most frequent adverse event reported by patients in the controlled clinical trials. However, the incidence of dry mouth reported during the double-blind, placebo-controlled periods of the Phase 2 and Phase 3 trials was similar among patients who received the transdermal patch containing either active oxybutynin or placebo. Hence, it is difficult to conclude that this event is solely reflective of an effect due to the medication. Furthermore, the incidence of dry mouth reported for patients using the transdermal delivery system was over 5-fold lower than the incidence reported by patients who were treated with oral oxybutynin at standard therapeutic doses. Hence, the transdermal delivery system, which greatly reduces systemic levels of DEO, an active metabolite of oxybutynin formed following oral dosing, provides a great improvement in side effect profile relative to anticholinergic side effects while maintaining efficacy. There were relatively few serious adverse events reported during the clinical trials, and none were considered related to drug treatment.

Similar safety trends were observed with MATRIX (Phase 4 study) and with the postmarketing data. Overall, the application site-related conditions, which are primarily irritation and inflammation responses to the topical patch and topical application of oxybutynin have consistently been the primary adverse event observed or reported with the use of Oxytrol. Most of these AEs are of mild to moderate intensity, and few have been reported as serious AEs. These events either self-resolve when the transdermal system is removed, or resolve with minimal intervention. Similar trend of anticholinergic adverse events was also observed with the post market use of Oxytrol. Dry mouth AE was reported as the most common anticholinergic-related adverse event in all clinical trials, as well as in spontaneous AE reporting databases (AERS and WHO Vigibase). Other AEs with a potential association with the drug's anticholinergic mechanism of action include blurred vision, constipation, dizziness, somnolence and dry throat and dry eyes. Overall most of these events, are of mild to moderate intensity, and resolved when medication was stopped. Furthermore, the overall incidence of anticholinergic

adverse events based on patient exposure is relatively low, and is lower than the expectation for these events with oral administration of oxybutynin.

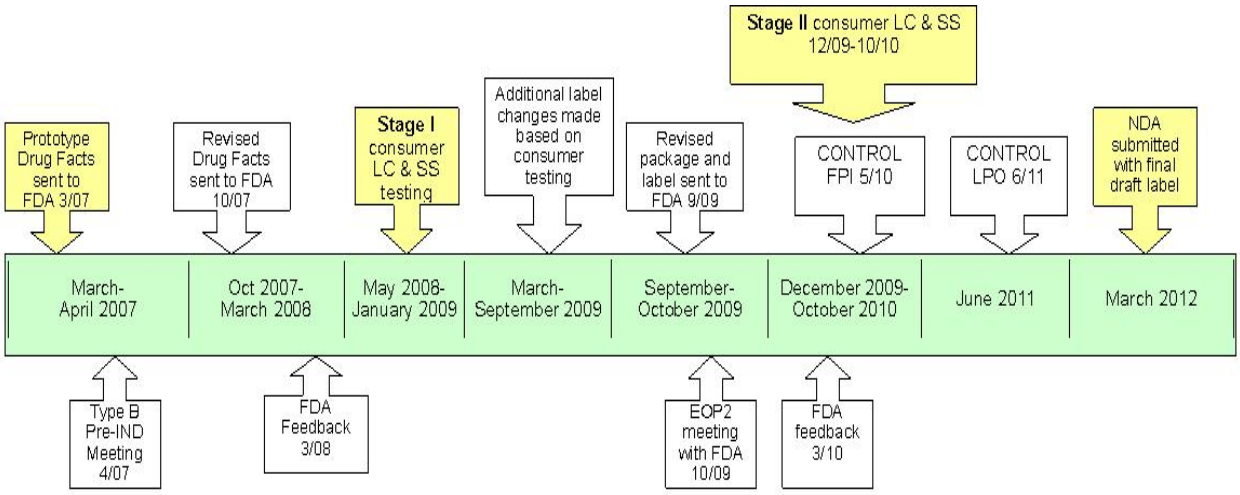
In conclusion, the clinical studies and the post market safety data demonstrate similar safety trends and support the overall safety of transdermal dosing of oxybutynin.

6.0 OVERVIEW OF THE OXYTROL OTC LABEL

6.1 Oxytrol Label Development

Merck Consumer Care began label development to support use of Oxytrol as a nonprescription medication in 2007 (Figure 5) and submitted the NDA to support nonprescription use on 26 March 2012. FDA guidance has been integral to the development and evaluation of the OTC proposed label, with FDA providing advice at all stages of OTC label development. The studies depicted in Figure 5 are described later in this section.

Figure 5 Key Events in Oxytrol OTC Label Development



6.2 Key Factors in Development of Oxytrol OTC Label

The rationale for developing Oxytrol for nonprescription use in treatment of OAB is outlined in the Executive Summary. The benefits and risks of OTC Oxytrol are summarized in Figure 1 Oxytrol Labeling Safeguards Paradigm.

To maximize the benefits, MCC designed labeling to support women in self-selection based on their OAB symptoms. Since current clinical guidelines for treatment of OAB recommend urinalysis in women that present to a physician with OAB symptoms, MCC developed OTC labeling that includes the signs and symptoms of other diseases that could produce urinary symptoms (e.g. DM, UTIs, BC and pregnancy). This OTC labeling directs women who think they may have signs or symptoms of these conditions to see a health professional.

As shown in Figure 1, MCC concluded that delay in diagnosis of UTI, DM, BC and pregnancy represented the most significant unintended risks of nonprescription Oxytrol. To maximize the net benefit of nonprescription Oxytrol by limiting the negligible risk, MCC took three steps in the proposed label. First, the proposed OTC label provides a description of each of the signs and symptoms of these conditions so that women with those symptoms are directed to see a health professional. Second, to reduce the likelihood of UTI or pregnancy as possible explanations for OAB symptoms, OTC labeling informs women that OAB symptoms need to be present for at least 3 months. Since UTIs tend to be acute in nature and undiagnosed pregnancy would be unlikely with 3 months or more of OAB symptoms, requiring 3 months or more of OAB symptoms should minimize risk. Finally, women are directed to stop using Oxytrol if there was no symptomatic improvement in 2 weeks or if symptoms worsen. With the possible exception of frequency, none of the other conditions that can cause urinary symptoms would be expected to respond to oxybutynin given its mechanism of action.

A summary of the initial Oxytrol OTC label elements that encourage accurate recognition and mitigate potential risk follows below. (The final proposed label is in Appendix 9)

1. Specific description of OAB symptomatology and a statement that one or more symptoms of urinary frequency, urgency, or urge incontinence were required to use Oxytrol.

2. OAB symptoms need to be present for at least 3 months.

3. Warnings to see or ask a doctor before use in certain situations:
   a. Urinary frequency could be an early sign of pregnancy, diabetes, bladder infection or another underlying condition
   b. Diabetes or excessive thirst
   c. Unexplained weight loss
   d. History of kidney stones
   e. Liver or kidney disease
   f. Narrow-angle glaucoma

4. Warnings to not use if:
   a: Male
   b: Under 18
   c: Pain or burning on urination, blood in urine, unexplained lower back or side, pain, or urine that is cloudy or foul smelling (women experiencing these symptoms are further also advised to see a doctor as soon as possible)
   d: Only have stress incontinence
   e: Urinary retention

f: Diagnosed gastric retention
g: Allergic to oxybutynin.

5. Ask a doctor or pharmacist before using Oxytrol if taking a prescription medication for OAB or taking a diuretic.

6. Stop use and ask a doctor if:
   h: condition worsens
   i: new symptoms develop
   j: condition does not improve after 2 weeks of use
   k: severe itchiness, blistering, or allergic reaction

6.3 Role of Consumer Research in Evaluating Proposed OTC Label

In order to learn if consumers are likely to be successful in self-managing a medication in an OTC setting, three types of studies are typically conducted. The first, label comprehension (LC), addresses whether or not consumers understand label messages. The second, self-selection (SS), is conducted to learn if consumers can appropriately select to use or not use the product, based on the labeling and their own health status. This type of study can also incorporate an assessment of how well consumers can self-recognize the condition. Finally, actual use studies are conducted to learn about how consumers manage use of the product over time. Actual use studies typically do not test the consumer's understanding of the label as in SS and LC studies, but seek to evaluate consumer behavior as they use the product.

As shown in Figure 5, consumer LC and SS studies were conducted iteratively throughout the label development process. Note that while it is important to define target thresholds during the planning phase of these studies, targets are informed goals in assessing success of the label messages being communicated and the behaviors elicited. The point estimates and ranges provide an overall measure of comprehension, decision-making and behaviors, rather than a binary measure where missing or achieving the target represents failure or success. Scores in these types of studies rarely reach 100% due to many factors such as respondent fatigue; interviewer error or interviewer bias; question ambiguity; and degree of attention the respondent is giving to the task, when there is often no downside to guessing or responding quickly in this single-visit research study. Typically, a score of 90% or higher is considered to be very good.

6.4 Stage I Initial Self-Selection and Label Comprehension Testing

The initial Oxytrol OTC label was tested in one label comprehension study and one self-selection/self-diagnosis study to evaluate its effectiveness at communicating messages regarding usage, cautions and warnings, and enabling women with OAB symptoms to self-select appropriately. Findings from these two studies led to modifications of the OTC label.

6.4.1 Protocol 82023: Initial Label Comprehension Study 2008

This initial label comprehension study evaluated comprehension of label messages (product use, directions for use, label warnings) among three general populations of women and whether men would understand that OTC Oxytrol was only for women. 675 subjects were enrolled into 4 separate cohorts, consisting of normal literate (NL) females who said they had OAB (N=196), low literate (LL) females who said they had OAB (N=204), general population (GP) of females without OAB (N=199) and a general sample of males (N=76). Once recruited, a Rapid Estimate of Adult Literacy in Medicine (REALM) test was administered to evaluate the subject's literacy in medicine (Davis, 1993). The subject was then given the product package to read. After reading the label, a comprehension questionnaire was administered by a trained interviewer. The questionnaire contained scenarios describing possible real-life situations in which subjects had to judge appropriate and inappropriate use of the product, based on their understanding of the product label. An example of a scenario question follows:

> *Harriet has overactive bladder that she has not started treating yet. When she went to the bathroom today she noticed there was blood in her urine. According to the label, is it okay or not okay for Harriet to use this product? Why do you say that?*

Asking a study respondent to evaluate scenarios such as this one requires that the respondent apply the information from the label instead of simply identifying whether or not the information is present.

Results of this LC study indicated that the initial label already demonstrated effective communication in many areas. Respondents demonstrated excellent comprehension of the product's use for treatment of OAB (96-100%) and showed strong understanding of OAB symptoms (83-91%). Recognition that symptoms that might indicate urinary tract infections or other more serious conditions preclude use also achieved high scores: blood in the urine (94%), lower back pain (91-95%) and pain when urinating (91-92%) were consistently understood. Males understood the message that the product is not for men (95%).

Several messages attained lower scores than desired, notably narrow-angle glaucoma (77-83%), stress incontinence (73-81%) and developing blisters and itchy skin when using the product (79%).

6.4.2 Protocol CL2008-19: Initial Self-Selection Study 2009

This study evaluated the ability of consumers to correctly self-recognize OAB and self-select the product based on product uses and warnings, in light of the consumer's unique and relevant medical history. 587 subjects with OAB symptoms were enrolled into three cohorts: NL (n=218) and LL general population (GP) women (n=137) and a mixed cohort of adults with at least one of four contraindicated conditions: being male (n=172), having diabetes (n=42), having glaucoma (n=12) or being pregnant or breast-feeding (n=10).

In the NL and LL cohorts, subjects demonstrated the ability to self-recognize the symptoms of overactive bladder compared to a physician's diagnosis. The scores of 89% of NL subjects and 91% of LL subjects were consistent with that of the physician. Similarly, the self-selection decision of 82% of NL subjects and 85% of LL subjects were consistent with the physician's assessment.

While these scores are strong, it is important to review the data from the subjects whose decisions were not consistent with that of a physician. In both the NL and LL cohorts, there were subjects who made one of two errors which carry little or no risk:

1. For the self-diagnosis measure, the subject did NOT feel she had OAB but the physician did. For the self-selection measure, the subject did NOT feel she should use the product but the physician felt she could. While this decision is inconsistent, there is no harm to the subject if she decides not to try the product even if she is eligible to do so.
2. The subject believed she had OAB but the physician felt that she had stress incontinence only. While this decision is inconsistent, there is minimal risk to the subject, as stress incontinence is a benign condition for which the product will not be effective.

When these factors are taken into consideration, the following conclusions can be drawn from Protocol CL2008-19 regarding the NL and LL cohorts:

1. 92% or more respondents in each of the two cohorts made a self-selection decision which was consistent with that of a physician or which was associated with minimal or no risk.
2. 95% or more respondents in each of the two cohorts made a self-diagnosis decision which was consistent with that of a physician or which was associated with minimal or no risk.

Looking now at the subjects in Cohort 3, which included subjects with at least one of four factors contraindicated on the label, self-selection scores were lower. Males attained a 72% score for correct self-selection, and the scores among respondents with diabetes, glaucoma, and pregnancy/breast-feeding were lower (24%, 33%, and 40%, respectively). It should be noted that of these four subgroups, being male was

the only "do not use," condition on the tested label. The others were "ask doctor." Also note that 11 of the 12 people with glaucoma reported later that they did not have "narrow angle" glaucoma but rather open-angle glaucoma which is not contraindicated. Additional label changes and studies were undertaken to address those weaker results.

6.5 Modifications of Oxytrol OTC Label

The findings from Protocols 82023 and CL2008-19 were discussed with the FDA in October 2009, as well as the design of additional consumer label studies and several changes in the proposed OTC label which had been made. The most notable changes in the label were as follows.

- Name changed from “Oxytrol” to “Oxytrol for Women” and the package color and graphics were modified to better communicate that the product is not for men.
- The warning for diabetes was removed, since diabetes is not contraindicated in the prescription label, and the message about undiagnosed diabetes symptoms was expanded.
- A statement informing women that urinary frequency could also be a symptom of undiagnosed pregnancy, diabetes, UTI, or other more serious conditions was enhanced with bold text and yellow highlighting.

The label that incorporated these changes was studied further in Stage II consumer research. The final proposed Drug Facts labeling text is in Section 6.7.7.

6.6 Stage II Consumer Research Findings with Oxytrol OTC Label

6.6.1 Self-Selection and Label Comprehension Research 2010

6.6.1.1 Protocol 92061: Self-Selection among Men

Protocol 92061 was a SS study among males with urinary symptoms to evaluate the effectiveness of the specific label warning, “do not use if you are male.” Potential respondents were screened and qualified respondents were directed to a market research site. At the site, subjects reviewed the package labeling and made a decision regarding whether the product was right for them to use or not. 571 males (354 GP plus 217 respondents augmented for low literacy) were evaluated for self-selection decisions. Over 90% of GP men and 90% of LL men self-selected appropriately. The score for GP men was a substantial improvement over the 72% score attained in the initial SS study described earlier in Section 6.4.2. Incorrect responses were generally related to the symptoms the product treats (e.g., “Because it’s a relief from active bladder problems”).

6.6.1.2 Protocols 92062 and 10054: Label Comprehension and Self-Selection Related to Pregnancy

Protocol 92062 was a LC study conducted in 574 women (350 GP, 224 augmented LL) who were of childbearing age and not surgically sterile, to evaluate the effectiveness of the enhanced label warning:

> "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."

93% of the GP women and 83% of the low literate GP women correctly comprehended the enhanced pregnancy warning.

Protocol 10054 was a targeted SS study among 435 pregnant women with urinary symptoms (308 GP, 127 augmented LL) to evaluate the effectiveness of the same specific undiagnosed pregnancy warning described above for Protocol 92062. Note that the label also states, "If pregnant or breastfeeding, ask a health professional before use."

92% of GP pregnant women correctly indicated that they should not use this product and/or would talk to a doctor first. The cohort of low literate women scored a lower 68%. However, as MCC had previously observed substantially higher label comprehension scores for the undiagnosed pregnancy message among low literate women (83% in Protocol 92062 described above), it is possible that the particular sample recruited for the self-selection study was atypical of this population.

6.6.1.3 Protocols 92099 and 10053: Label Comprehension Related to Diabetes

The objective of label comprehension Protocol 92099 was to evaluate comprehension of the label messages associated with undiagnosed diabetes (i.e., consult a physician before using if you have a family history of diabetes or if you have frequent urination with excessive thirst, extreme hunger or increased tiredness) among a general population. The data show that 93%-94% of GP females demonstrated the ability to comprehend the two scenarios related to undiagnosed diabetes. Scores among the LL cohort were lower, at 79% and 71%.

LC Protocol 10053 explored comprehension of the same warnings in 160 respondents who were 44 years or older, with some risk for diabetes. Among this population, 89% understood the family history scenario and 88% understood the pre-diabetes symptom scenario.

6.6.1.4 Protocol 92101: Label Comprehension among Women 65+

The objective of this LC study was to evaluate comprehension of the label messages among 350 women who were 65 years old or older. While the FDA did not require an LC study for this population, MCC evaluated comprehension among a sample of older women with OAB symptoms, since older women are likely to be key users of OTC Oxytrol.

The results of this study show that nearly all of the most important messages communicated effectively at levels over 80% and in many cases over 90%. In particular, strong scores were achieved on directions for use, warnings related to possible UTI symptoms, allergies to the medication and several others which could indicate a different medical problem, such as diabetes.

6.6.1.5 Protocol 10053: Pivotal Label Comprehension

While the prior consumer studies were conducted iteratively for label development, the goal of the Pivotal study was to obtain reliable estimates of comprehension among the target population, using a label which had been modified during the course of the development program.

This study was conducted in 592 women (472 GP and 120 augmented LL). Most key messages were effectively communicated, meeting or narrowly missing their objectives. Two key messages exceeded the 90% lower bound (LB) for success: “allergic to oxybutynin” (LB 92.8%) and allergic reaction (LB 90.6). Four communication objectives did not meet the lower bound threshold but were within 6 points: urinary retention (LB 88.4%), gastric retention (LB 86.7%), developed blisters and red itchy skin (LB 85.3%), and narrow angle glaucoma (LB 84.4%). The lowest scoring scenario was stress incontinence (LB 73.3%), which is a benign condition for which Oxytrol will not work and which was therefore a communication objective with lower medical consequence. This scenario attained an actual score of 77%. In most cases, the LL cohort scored within 10 points of the GP.

Of note, improvement was seen for several messages between the 2008 Label Comprehension study (Protocol 82023) and this study, such as improvements in scores among NL respondents in messages for kidney stones, narrow-angle glaucoma, severe skin reaction, and oxybutynin allergy. Labeling and questionnaire improvements likely factored into these positive changes in scores.

6.6.2 Conclusions from Label Comprehension and Self-Selection Studies

- The messages regarding directions for use and the key safety warnings are well understood by the broad target population as well as important cohorts, including women of childbearing age, women 65 years and older, and women who might be at some risk for diabetes. Low literate respondent scores were generally within 10 points of the scores for the GP.
- The important warning messages about symptoms of UTI and possible allergic reactions to the medication attained especially strong comprehension scores among elderly women.
- Label comprehension scores demonstrated improvement in some areas versus the earlier study using the original label, indicating that changes made over time may have helped to improve label effectiveness.
- Self-selection studies have demonstrated effective label communication among general populations of women with OAB, including those of low literacy, and among the cohorts of men and pregnant women (over 90% appropriate SS in all). While low literate pregnant women did not score well, the sample may have been atypical of low literate subjects, since comprehension scores among low literate women in another study were stronger. To strengthen the label, however, the female icon has been redrawn to avoid an association with pregnancy.

6.7 CONTROL Study: Actual Use Testing

6.7.1 Study Methods

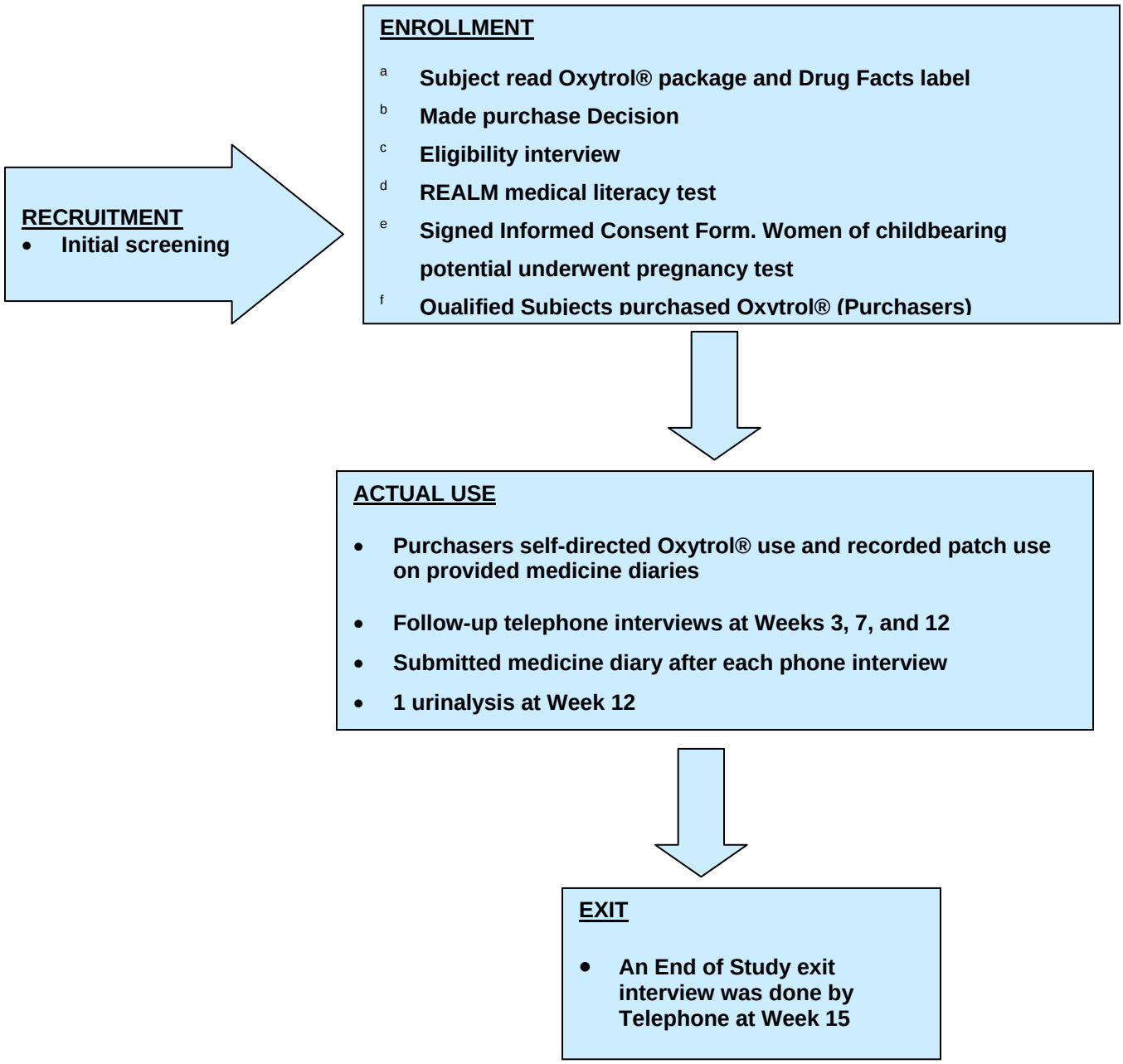
6.7.1.1 Study Design

The CONTROL study was an observational, open-label, 15-week study designed to evaluate ongoing use behavior in subjects who represent potential consumers of Oxytrol for Women. Subjects were recruited to 26 retail pharmacies in 10 metropolitan areas in the United States.

Figure 6 shows the four phases of the study:

1. An initial recruitment phase that included a screening telephone interview
2. An onsite enrollment phase that consisted of a purchase decision and a medical history interview
3. A 12-week actual use phase that included telephone follow-up interviews. Subjects also recorded Oxytrol use in diary cards
4. A final end-of-study interview

Figure 6 Diagram for Subject Recruitment and Study in CONTROL



Women of Childbearing Potential

Women with OAB symptoms were recruited via newspaper, direct mail, TV, radio and flyers placed in the participating retail pharmacies. Interested subjects called a call center or spoke with a participating pharmacy for screening.

Screening Criteria

- Female
- 18 year of age or older
- Not pregnant
- Never trained or employed as health care professional
- No one in household employed in pharmaceutical or in healthcare industry
- No participation in any research study in the past 12 months

Subjects without medical exclusion criteria could enter the 12-week use phase after providing informed consent and having a negative pregnancy test (women of childbearing potential). The minimal exclusion criteria allowed for an "all-comers" population and allowed ongoing use to be studied among women who were not completely eligible per the label.

Women meeting screening criteria could then participate in an onsite enrollment interview at the participating pharmacy. The subject was provided with the Oxytrol package and asked if they wanted to purchase the product for their own use. Subjects were informed of the cost of the product (which was reduced from $10 to $5 to increase enrollment relatively early in the study (N=127 verified users prior to change). The interviewer collected information pertaining to the subjects' OAB condition, medical history and determined the subjects' eligibility to participate and use Oxytrol in the study. Following the enrollment interview, all subjects completed the REALM test to determine literacy level, provided informed consent, and women of childbearing potential were given a pregnancy test. Subjects were compensated for participating in this part of the study.

Subjects with any of the following medical criteria were excluded from purchasing Oxytrol and participating in the 12-week use phase. To make the study as inclusive as possible, only conditions that would pose a medical risk to subjects could result in their exclusion. The minimal exclusion criteria allowed for an "all-comers" population and allowed ongoing use to be studied among women who were not completely eligible per the label.

- Narrow angle glaucoma
- Pregnant or Breast feeding

- Allergic to oxybutynin
- Blood in urine
- Back pain and fever with frequency, urgency, dysuria, hematuria, or cloudy urine

Use Phase

Subjects without medical exclusion criteria could enter the 12-week use phase after providing informed consent and having a negative pregnancy test (women of childbearing potential). The minimal exclusion criteria allowed for an "all-comers" population and allowed ongoing use to be studied among women who were not completely eligible per the label.

Subjects who completed the drug purchase procedure received one or more Oxytrol packages (as purchased), which included the Drug Facts label, and blank medication diaries. Subjects were not given instructions on product use (how to apply the patch) by pharmacy staff. However, subjects were trained on medication diary entry and were informed that they could return to the pharmacy at any time during the 12-week use period to purchase additional drug. Per protocol, subjects were not told they could purchase a maximum total of 96 patches (24 boxes with 4 per box). Subjects were requested to return to the pharmacy at week 12 for a urinalysis and then at week 15 for the end of study interview.

Three follow-up phone interviews were conducted by trained personnel at weeks 3, 7, and 12 from the enrollment visit. All interviews conducted utilized standardized scripts and focused on the following:

- Whether the subject had used Oxytrol since her initial purchase (asked at the subject's first follow-up interview) or since her last follow-up interview (asked at Weeks 7 and 12).
- Whether the subject's OAB condition had improved, stayed the same, or worsened at 2 weeks after starting the study compared to before the subject started the study, (asked at the subject's first follow-up interview) or as compared to the last follow-up interview (asked at Weeks 7 and 12).
- Whether the subject had developed any new urinary symptoms (urinary frequency, urinary urgency, urge incontinence, or other) since the initial purchase (asked at the subject's first follow-up interview) or since her last follow-up interview (asked at Weeks 7 and 12).
- Whether the subject had developed any of the new symptoms in Table 7 since the initial purchase (asked at the subject's first follow-up interview) or since the last follow-up interview (asked at Weeks 7 and 12). These symptoms were listed on the Case Report Form but subjects were not shown the list. Interviewers selected an appropriate symptom based upon subject response.

- Whether the subject had stopped using Oxytrol because of her unimproved OAB condition (i.e., worsening or staying the same) or because of newly developed symptoms where the label directed them to stop use or talk to a doctor as listed in Table 7.
- Whether the subject had consulted with her doctor about her unimproved OAB condition (i.e., worsening or staying the same) or because of her newly developed symptoms as listed above. And if so, what was the doctor's recommendation of whether she should continue using Oxytrol.
- Whether subjects had experienced any AEs other than those relating to new symptoms listed in the follow-up visits.

Table 7 CONTROL: Listing of New Symptoms Indicating Subject Should Stop Use or Talk to Their Doctor or Health Professional

Allergic reaction to the patch	Liver or kidney disease
Began taking a diuretic	Lower back pain (unrelated to injury)
Bladder infection	Narrow-angle glaucoma
Blood in the urine not related to menses	Pain or burning when urinating
Cloudy urine	Severe redness, itchiness or blistering at the site of application
Flank (side) pain	Unable to empty bladder completely (urinary retention)
Foul-smelling urine	Unexplained weight loss
Frequent urination with excessive thirst, extreme hunger or increased tiredness	Urinary tract infection
Gastric retention	Became pregnant
Kidney stones	
Additional symptoms of note included diabetes, chills, fever, and glaucoma but did not require a subject to stop use or talk to a doctor. Abdominal pain and pelvic pain as new symptoms were added by the FDA but were not on the Drug Facts label. Source: CONTROL CSR Section 11.1.1	

6.7.1.2 Label Effectiveness Endpoints and Definition of Success

The primary endpoint was the rate of incorrect use defined as the proportion of Oxytrol users who did not stop use after any of the following occurred:

- Development of a new symptom where the label directed the consumer to talk to their doctor or discontinue use.
- Worsening of the initial OAB symptoms that prompted purchase.
- Development of new symptoms of abdominal or pelvic pain (not listed in OTC label used in the study as an instruction to stop use or talk to the doctor but was added mid-study to the endpoint as suggested by the FDA). Additional questions were not posed to subjects; this did not affect the conduct of the study.

The incorrect use rate was calculated by dividing the number of subjects in these categories by the total number of subjects in the verified user population, and the 95% confidence interval (CI) was constructed. As suggested by the FDA, the upper 95% CI should be less than 5% for a successful outcome. [Note: A verified user is a subject who had follow-up interview and diary data to support her Oxytrol use].

Secondary endpoints (SE) were defined as follows at the request of FDA:

SE1: The proportion of verified users who did not stop use when their condition worsened or when they developed a new symptom referred to in the labeling (was the original primary endpoint and excluded subjects who reported abdominal/pelvic pain).

SE2: The median time taken to discontinue Oxytrol use by verified users who did not experience improvement in their symptoms after two weeks of treatment. (only included subjects who had used Oxytrol for 2 weeks)

SE3: The proportion of verified users who did not stop Oxytrol use within two weeks after experiencing no improvement in their symptoms. (This only included subjects who had used Oxytrol for 2 weeks.)

SE4: The medical risk (as defined a priori in the protocol) of the verified users who had a condition or symptoms as described in Primary Endpoint or Secondary Endpoint No. 1. For secondary endpoint 4, the risk classification shown in Table 20 was used.

For example, patients with signs and symptoms of UTI were defined as at some medical risk while patients with OAB symptoms that did not improve were defined to have minimal risk.

SE5: Proportion of verified users who misused the patch (incorrect duration of use or simultaneous use).

SE3&5: This was a combination of SE3 and SE5: Proportion of subjects who did not stop use when they either developed a new symptom or when their condition did not improve (worsened or stayed the same) – with the addition of abdominal or pelvic pain.

6.7.1.3 Clinical Review for Evaluation of Subject Responses

In CONTROL, there were different types of questions which generate different types of data, close-ended or open-ended. Close-ended data have pre-defined responses to questions, such as whether or not a woman has urinary frequency. The response is yes or no and is very easy to analyze. In this study, up to 1000 closed-ended data points could have been collected per subject through interviews and diary cards.

In contrast, open-ended data are generated by questions that cannot have pre-defined response categories. In CONTROL, the most valuable open-ended data came from AE narratives, which provided additional information regarding worsening of OAB symptoms and all symptoms which the label directed the subject to stop use or talk to a doctor. Subjects were asked up to 40 additional open-ended questions. For example, subjects were asked why they continued to use Oxytrol if their OAB symptoms stayed the same or worsened. These types of responses are free-flowing and can be quite varied. They are generally difficult to program and need to be reviewed on an individual basis in order to fully understand a subject's behavior.

Programmatic rules were established to capture all possible incorrect use behavior. Subjects were identified as potential misusers if they developed any symptoms referred to in Table 7 or developed a worsening of their OAB and applied another patch after the onset of the new symptoms. Additional information such as talking to the doctor, duration of symptoms, or severity of new symptoms was not considered at this level of programming.

Mitigation/Adjudication Process

In order to best capture the intent of the primary endpoint and to identify behavior that could potentially place a consumer at risk there was a need to develop an adjudication process referred to as mitigation. One example that illustrates the need to conduct mitigation is if a subject talked with her doctor. If a woman talks with her doctor and seeks treatment for new symptoms as directed on the label but continues using the product, she is displaying appropriate behavior. However, the programmatic algorithm did not consider the “talk to doctor” factor, in order to capture all potential misusers. If all women who spoke with their doctor were counted as acceptable, women may have been tabulated as correct if they did not follow their physicians' advice or waited a month before talking with their doctor. This would have missed subjects that should have been considered misusers.

It was possible for subjects to make multiple types of errors during the study, including:

- Continued use of Oxytrol when OAB condition worsened or subject developed a new symptom referred to on the labeling (primary endpoint)
- Continued use of Oxytrol when OAB condition did not improve after two weeks
- Incorrect use of the patch (i.e. simultaneous use of more than one patch or incorrect duration of patch use, >4 days)

Each time a subject made an error of these types, data from their full Case Report Forms (especially open-ended responses) were closely reviewed to understand if the subject really had incorrect ongoing use behavior. In addition, for SE5, all diary card records were individually reviewed.

Criteria for relevant endpoints were established as guidelines for mitigating this consumer behavior data. Therefore, meaningful results could only be obtained when all of the relevant data were applied. This allowed a subject's behavior to be classified as correct or incorrect for a specific endpoint.

MCC reviewed subject data for all subjects programmatically captured as possible misusers for the primary endpoint and secondary endpoints 1, 3, and 5. For the primary endpoint and secondary endpoint 1, three independent external physicians with training in urology and urogynecology and one sponsor physician with experience in use studies evaluated all subject data. A similar process was conducted for secondary endpoints 3 and 5 by sponsor clinical research personnel.

Considerations when establishing the mitigation process are included in the FDA Self-Selection Study Guidance and FDA Label Comprehension Study Guidance. Actual Use Study Guidance has not yet been published.

Mitigation was conducted as follows. For the primary endpoint, subjects identified as having a new symptom or a worsening of OAB symptoms were identified by search of the CRF database. New symptoms defined by the label instructed the user to stop use or talk with their doctor were defined as listed in Table 7. These terms may not have been stated by the subject but were classified this way by the nurse interviewer based on this predefined list of conditions.

All subjects who reported one of these symptoms listed in Table 7 or reported that their OAB symptoms worsened and did not stop using the patch were reviewed by each physician to determine if the subject should have discontinued Oxytrol or whether there were mitigating factors that justified the subject's continued use of the patch. For example, if a subject recognized UTI symptoms and sought treatment and was told by her physician to continue using Oxytrol, the subject was considered to have correct use for the final analysis.

All subjects who reported one of these symptoms listed in Table 10 or reported that their OAB symptoms worsened and did not stop using the patch were reviewed by each physician to determine if the subject should have discontinued Oxytrol or whether there were mitigating factors that justified the subject's continued use of the patch. For example, if a subject recognized UTI symptoms and sought treatment and was told by her physician to continue using Oxytrol, the subject was considered to have correct use for the final analysis.

6.7.1.4 Sample size Estimation

The study was powered to find an incorrect use rate (primary endpoint) by requiring the upper 95% CI to be less than 5%, which requires at least 531 verified Oxytrol users.

During the study, 727 subjects reported use of Oxytrol on diaries and in follow-up interviews, making them verified users. Considering the null hypothesis of greater than 5% incorrect use rate and given an alternative incorrect use rate of 2.5%, this sample size can provide a power of 97%.

6.7.2 Description of Study Population

6.7.2.1 Subject Recruitment and Enrollment

There were 2731 subjects who responded to advertising and underwent an initial telephone screening. The study recruitment ad was directed at women, but it did not include product labeling. Of this group, 1230 subjects entered the enrollment phase and visited one of the study sites, and 1218 completed the enrollment interview. The enrollment interview was not conducted until the subject had evaluated the Oxytrol package, which included the *Drug Facts Label,* and made a purchase decision.

Table 8 summarizes reasons for failing the telephone screening interview. The 561 excluded via the telephone screen included 5 women (0.02%) who might have been pregnant and 45 men (1.7%). The most common reasons classified as "Other" were trained as healthcare professionals (363/2731, 13.3%), employed by a healthcare practice (81/2731, 3%), previous participation in any market research study, product label study or clinical trial in the past 12 months (108/2731, 4%), and employed by a managed care or health insurance company as a healthcare professional (50/2731, 1.8%). As is typical of use studies, a high percentage of subjects who passed the screening phase did not arrive at the pharmacy site.

Table 8 CONTROL: Summary of Subject Recruitment and Enrollment

	N (%)
Responded to recruitment ad	2731 (100.0%)
Failed telephone screening inclusion/exclusion criteria	561 (20.5%)
Male	45 (1.7%)
Pregnant or might be pregnant	5 (0.2%)
Other	511 (18.7%)
Passed all telephone screening questions	2170 (79.5%)
Appeared at pharmacy and for enrollment visit	1230 (45%)
Completed the enrollment interview	1218 (44.6%)
Decided not to Purchase Oxytrol	149
Decided to Purchase Oxytrol	1069

Source: CONTROL CSR Table 4

6.7.2.2 Reasons for Exclusion from Use Phase

Of the 1069 subjects who decided to purchase Oxytrol, 214 were excluded from participation while 855 were dispensed Oxytrol. Of the 214 excluded from use phase, most (181) were excluded for non-medical reasons (Table 9). The medical exclusion criteria were recommended by the FDA.

Of the 2.5% (27 of 1069) excluded for medical reasons, hematuria was the most common reason for exclusion (13 subjects). Three subjects were excluded for having back pain and fever and one of the following: dysuria, hematuria or cloudy urine. This UTI definition was highly specific so that subjects with evidence suggesting pyelonephritis were excluded. Subjects with isolated dysuria and no other symptoms, for example, were allowed to enter the use phase.

Table 9 Summary of Subjects Excluded from Use Phase

Decision to Purchase Oxytrol	1069
Oxytrol dispensed	855 (80.0%)
Excluded for non-medical reasons	181 (16.9%)
Refused Pregnancy Test	12 (1.1%)
Did Not Sign Informed Consent	140 (13.1%)
Did Not Provide Contact Information	2 (0.2%)
Did Not Purchase Drug	37 (3.5%)
Excluded for a medical exclusion	27 (2.5%)
Narrow-angle glaucoma	4 (0.4%)
Blood in urine	13 (1.2%)
Pregnant	0
Breastfeeding	5 (0.5%)
Known allergy to oxybutynin	4 (0.4%)
Back pain and fever and one of the following, dysuria, hematuria and cloudy urine	3 (0.3%)
Excluded, Other Reasons[a]	6 (0.6%)

[a] Consent and Measurements CRF was not completed and no additional data was collected for these individuals

In an OTC setting, the women who were medically excluded in CONTROL would not have study safeguards to prevent them from buying Oxytrol. Thus, it is important to understand these subjects in order to determine if there would be real-world risk to subjects in these populations.

Narrow Angle Glaucoma

Oxytrol, and other anticholinergic medications, are contraindicated in patients with uncontrolled narrow angle glaucoma because it can increase intraocular pressure, precipitating an acute attack of glaucoma. Subjects in CONTROL were excluded from use if during the enrollment interview they reporting having narrow angle glaucoma. The following four subjects responded that they had been diagnosed by their physician with narrow angle glaucoma. The enrollment questionnaire did not ask if their narrow angle glaucoma was controlled or uncontrolled. However, since these subjects had been diagnosed with narrow angle glaucoma, which can only be done by a physician, it is unlikely that their narrow angle glaucoma was uncontrolled. As noted below in Table 10, one subject specifically stated that she was being treated for her narrow angle glaucoma and two subjects have previously taken other OAB medications.

Table 10 Subjects Excluded at Enrollment for Narrow Angle Glaucoma

12-0037	Excluded at enrollment after reporting that she had narrow angle glaucoma. Narrow angle glaucoma was diagnosed by a doctor and is treated. Subject reported OAB symptoms for 3 years and also has stress incontinence. She wanted to use patch "to help control my frequent urination."
25-0027	Excluded at enrollment after reporting that she had been diagnosed with narrow angle glaucoma and blood in her urine. She was diagnosed with OAB by her physician and has had OAB symptoms for 3 years with incontinence. She was on a bladder medication previously but can no longer afford it. She "thought maybe I could try to see if I could benefit from this product."
34-0025	Excluded at enrollment after reporting that she had narrow angle glaucoma. Dr. had said "it was okay for her to use OAB medications." She reported OAB symptoms of frequency for 30 years and urgency and incontinence for 10 years and was told by her Dr. that she had OAB. Her eye Dr. had checked her eyes when she was on Detrol and some other medications and she indicated that her doctor okayed use of medications.
37-0104	Excluded at enrollment after reporting that she had narrow angle glaucoma and that she was diagnosed by a Dr. She had OAB symptoms for at least 4 years including incontinence but did not have a Dr. diagnosis of OAB. She wanted to use the patch "because I pee a lot and am tired of it and because she has a overactive bladder."

Breastfeeding

It is not known whether Oxybutynin is excreted in human milk, and caution should be exercised when nursing mothers use Oxytrol. The proposed Oxytrol Drug Facts label states that women who are breastfeeding should talk to a doctor before use. Women in CONTROL were excluded if they reported that they were breastfeeding and the following four women in CONTROL reported that they were breastfeeding (shown in Table 11). These subjects were not asked follow-up questions including if they were planning on talking to their doctor before use or if they were planning to stop breastfeeding prior to using the medication.

Table 11 Subjects Excluded at Enrollment for Breastfeeding

17-0080	Subject (42 years old) was excluded at enrollment after reporting that she was breastfeeding. She reported having OAB symptoms for 3 years without incontinence but was not diagnosed by a doctor.
19-0109	Subject (39 years old) was excluded at enrollment after reporting that she was breastfeeding. She reported having frequency, urgency, and incontinence for 6 years but was not diagnosed by a doctor.
25-007	Subject (23 years old) was excluded at enrollment after reporting that she was breastfeeding. She reported having OAB symptoms for 1 year without incontinence but was not diagnosed by a doctor.
28-0035	Subject (31 years old) was excluded at enrollment after reporting that she was breastfeeding. She reported having OAB symptoms for 8 years with incontinence but was not diagnosed by a doctor.
35-0014	Subject (49 years old) was excluded at enrollment after reporting that she was breastfeeding. She reported having OAB symptoms for 8 years with incontinence but was not diagnosed by a doctor.

Allergy to Oxybutynin

Women who self-reported an allergy to oxybutynin were medically excluded from CONTROL. As shown in Table 12, one subject (10-0088) confused allergy with side effects. Physician follow-up information was not collected for these subjects to understand if these subjects really were allergic to Oxybutynin. Allergies to oxybutynin are very rare.

Table 12 Subjects Excluded at Enrollment for Allergy to Oxybutynin

10-0088	Excluded at enrollment after reporting that she was allergic to oxybutynin. However, subject later stated that she did not think of allergy until the pharmacist told her she could have blurriness, dry mouth, and constipation as I did with Enablex and Vesicare. Subject reported that she was diagnosed with OAB by her doctor and had symptoms for 2 years.
12-0058	Excluded at enrollment after reporting that she was allergic to oxybutynin. She indicated that she did not see the allergy warning and would try almost anything to help control her bladder problem. Subject reported that she had OAB for 30 years and incontinence and also indicated her doctor had told her she had OAB.
15-0056	Excluded at enrollment after reporting that she was allergic to oxybutynin. She stated that she did not notice the allergy warning on the label. She is currently taking Vesicare and was diagnosed with OAB by her physician. She reported having symptoms of OAB for 10 years and incontinence for 5 years. Her OAB has been diagnosed by a physician.
33-0034	Excluded at enrollment after reporting that she was allergic to oxybutynin. OAB symptoms of urgency and incontinence for 10 months. Did not know that oxybutynin was the active ingredient.

Hematuria

Women with blood in their urine were excluded from the use phase of the study because blood in the urine could potentially be a symptom of UTI or bladder cancer. As displayed in Table 13, thirteen subjects in CONTROL were excluded after self-reporting blood in their urine at enrollment. Women who reported this were asked follow-up questions at the enrollment visit and were recommended to see their physician or HCP.

Nine of these 13 (70%) women reported having blood in their urine for 1 month or longer. Five of the nine women went to their physicians for follow-up visits. Two of the five were diagnosed with conditions of concern. One subject (15-0050), reported blood in her urine and symptoms of UTI for 3 months or longer and was diagnosed with UTI and Type 2 diabetes. The other subject (33-0008) reported blood in her urine for 2 months at enrollment and went for follow-up 7 months later and was diagnosed with a UTI and OAB at that time. The other three subjects' physicians reported that their patients either had no underlying health condition (27-0011), had long-standing, treated conditions causing symptoms (12-0010), or the blood was

caused by a renal cyst (21-0050). Two of the nine subjects said they would not go to their doctor after hearing the site's recommendation because they did not feel it was necessary (25-0027, 37-0094). The two additional subjects reported blood in their urine for 5 and 6 months respectively and do not have any additional information.

One of the thirteen subjects reported blood in her urine for 14 days but upon follow-up was told by her physician it was in fact excessive menstrual bleeding.

The other three subjects reported the blood in their urine for one or two days. These subjects are of greater consideration to the Oxytrol OTC program because they could potentially delay appropriate care, causing a progression of an underlying condition. One of these three subjects had already been planning on seeing a urologist (21-0148), one would not go to a physician because she does not have health insurance (28-0034), and one provided no additional information (17-0123).

Table 13 Subjects Excluded at Enrollment for Hematuria

12-0010	Excluded at enrollment after reporting blood in her urine which upon follow-up enrollment questioning said she had for 5 years. She is under a doctor's care. She had other symptoms including lower back pain, cloudy urine, and foul-smelling urine for 5 years. She saw her physician who reported that her symptoms are long standing chronic conditions for which the subject is being treated. Subject reported having OAB symptoms for 3 years.
15-0050	Excluded at enrollment after reporting blood in her urine for 3 months. She also reported unexplained weight loss for 6 months, lower back or side pain for 4 months, foul smelling urine for 6 months. Regarding the blood in urine the subject stated that she only had blood in her urine twice and it was a while ago. She did follow up with her doctor and was diagnosed with Type 2 Diabetes and a UTI. Upon treatment other symptoms resolved but she still reported urgency and frequency. Subject had been previously diagnosed with OAB by her physician.
16-0075	Excluded at enrollment after reporting blood in her urine and a compilation of UTI symptoms. During follow-up enrollment questioning, she reported that she had blood in her urine for 5 months, pain and burning upon urination for 4 months, fever and chills for 7 days, lower back or flank pain for 6 days, and foul smelling urine for 6 days. Subject stated that the blood was detected ~ 5 months earlier and there was no blood currently. She stated her back pain was from falling last week. This subject did not provide any follow-up information from her doctor. Subject reported that she had urinary frequency for 2 years and urinary urgency and incontinence for 4 months.
17-0123	Excluded at enrollment after reporting blood in her urine for 2 days. She also reported pain and burning while urinating and lower back pain for 2 days. This subject provided no additional information and it is unknown whether or not she went to her doctor. This subject had physician diagnosis of OAB and reported having OAB symptoms for 1 year with incontinence.
21-0014	Excluded at enrollment after reporting blood in her urine for 14 days. She went to her physician for follow-up which revealed she had excessive menstrual bleeding, which has since resolved. Subject reported frequency and urgency for 20 years and incontinence for 6 months.

21-0050	Excluded at enrollment after reporting blood in her urine for 3 years. She stated that she did not think it was important that she had blood in her urine since she had it for so long. Her physician said her UA was normal and blood may have been caused by a renal cyst and that she may have urinary retention. He prescribed oral formulation anticholinergic. The woman had OAB symptoms for 3 years and had been diagnosed with OAB by her physician.
21-0148	Excluded at enrollment after reporting blood in her urine for 1 day and other symptoms of UTI for 7 days to 3 years. Very little follow-up information is available for this subject other than that she has been planning on seeing a urologist. The subject was diagnosed with OAB by her physician and has experienced symptoms for 2 months.
25-0027	Excluded at enrollment after reporting blood in her urine for 3 years. She stated that it was random for her to have blood in her urine, she had some blood a week ago, but hadn't had any since 1 year ago and she thinks she's okay. Subject also stated that she was on previous bladder medication but can no longer afford it so she thought she could still try and see if she could benefit from this product. Subject reports experiencing urinary urgency and incontinence for 3 years and urinary frequency for 2 years. She was diagnosed with OAB by a physician. She has not gone to a doctor for the blood in her urine because she does not have health insurance. She does not plan to go to see a doctor, although she understands that she should. Subject was also excluded for narrow angle glaucoma.
27-0011	Excluded at enrollment after reporting blood in her urine for 1 year. Subject was seen by her doctor and after conducting multiple tests, reported that there were no underlying health conditions. The subject had OAB symptoms for 3 years and had been diagnosed with OAB by her physician.
27-0035	Excluded at enrollment after reporting blood in her urine for 6 months. This subject did not have any additional follow-up information regarding blood in her urine. She reported having OAB symptoms for 6 months.
28-0034	Excluded at enrollment after reporting blood in her urine for 2 days. Subject also reported pain and burning while urinating for 1 month. She stated that she will not go to her doctor for follow-up because she does not have health insurance. She was diagnosed with OAB by her doctor and reported having symptoms for 2 months.

33-0008	Excluded at enrollment after reporting blood in her urine for 2 months. She indicated that she thought the blood was only barely there. She had reported OAB symptoms for 5 years with incontinence. Subject went to doctor 7 months after her enrollment visit and was diagnosed with UTI and also told that she has OAB
37-0094	Excluded at enrollment after reporting blood in her urine for 1 month. She also reported: pain and burning, fever, and chills for 2 months; cloudy urine for 3 months; foul smelling urine for 3 year. She indicated she did not go to a doctor because she was not bleeding anymore so she did not feel it was necessary. She wanted to use patch because 'I thought it might be of help for the symptoms I have and it would be better to use it.'

Compilation of UTI Symptoms

Compilation of UTI Symptoms is defined as having back pain and fever and one of the following: dysuria, hematuria, or cloudy urine.

As displayed in Table 14, three women in CONTROL were medically excluded for having a compilation of UTI symptoms, which could indicate a more serious UTI that could potentially progress. Unfortunately, there is not follow-up data for any of these women. As shown below, two of the women had symptoms for months, while one had varying symptoms for one week to one year.

Table 14 Subjects Excluded at Enrollment for Compilation of UTI Symptoms

16-0075	Excluded at enrollment for a compilation of UTI symptoms. During follow-up enrollment questioning, she reported that she had blood in her urine for 5 months, pain and burning upon urination for 4 months, fever and chills for 7 days, lower back or flank pain for 6 days, and foul smelling urine for 6 days. Subject stated that the blood was detected approximately 5 months earlier and there was no blood currently. She stated her back pain was from falling last week. This subject did not provide any follow-up information from her doctor. Subject reported that she had urinary frequency for 2 years and urinary urgency and incontinence for 4 months.
37-0038	Excluded at enrollment for a complication of UTI symptoms. During follow-up enrollment questioning, she reported that she had pain and burning upon urination for 7 days, fever and chills for 7 days, lower back for 1 month, foul smelling urine for 1 year, and a feeling that she can't empty bladder completely for 14 days. She indicated that "she missed that on the package" referring to the message not to use the patch. Subject said her symptoms improved and she did not go to a doctor for follow-up visit. OAB symptoms for 3 month including incontinence
37-0164	Excluded at enrollment for a compilation of UTI symptoms. During follow-up enrollment questioning, she reported that she had fever 2 months, lower back for 2 months, cloudy urine for 4 months, and a feeling that she can't empty bladder completely for 1 year. Subject would not respond to follow-up calls. She had OAB symptoms for 1 year including incontinence. She said yes to purchase "because I thought it might be of help for the symptoms I have and it would be better to use it."

6.7.2.3 Description of Subjects Participating in the Use Phase

Of the 855 subjects who were dispensed Oxytrol, 785 reported use of the patch in follow-up interviews or on diaries while 70 decided not to use the patch after taking the package home. Of the 785 reported users, 727 recorded use in diaries and were considered as verified users, and 58 reported use only in an interview (non-verified users).

Completion rates for follow-up and exit interviews were high. Of the 785 possible users, 741 (94.4%) completed the week 3 interview, 719 (91.6%) completed the week 7 interview, and 693 (88.3%) completed the week 12 interview. Overall, 703 users completed the exit interview including 19 non-users. Only 31/785 (3.9%) were lost to follow-up.

Compliance with return of the medication dairies ranged from 728 (92.7%) for diary # 1 to 435 (55.4%) for diary # 3. Slightly over half of the subjects (453; 57.7%) returned to the pharmacy to provide a urine sample for testing. This included 443 verified users, 10 non-verified users, and 8 nonusers.

The 727 verified users had similar demographic characteristics when compared to the full population of evaluators, which includes subjects who decided not to purchase and those excluded from purchase (Table 15). The mean age in the verified use group was 58.4 years, with 16.6% of subjects 75 years of age or older. Approximately 70% had some college education and 77.2% reported their race as white. Based on the REALM literacy in medicine test, 12.2% were classified as low literacy.

Table 15 CONTROL: Demographic Characteristics of Verified Users

	Evaluators (N = 1218)	Verified Users (N = 727)	Rejected from Purchasing (N = 214)	Non-Purchasers (N = 149)
Race and ethnicity				
White	886 (72.7%)	561 (77.2%)	131 (61.2%)	104 (69.8%)
Black or African American	140 (11.5%)	66 (9.1%)	34 (15.9%)	19 (12.8%)
Hispanic or 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				
8th 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 or 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 (15.0)	56.1 (16.7)	61.2 (16.8)
Median	58	58	56	61
Range	18 - 94	18 - 94	18 - 92	18 - 92
Age groups				
18-20	13 (1.1%)	3 (0.4%)	2 (0.9%)	3 (2.0%)
21-30	57 (4.7%)	31 (4.3%)	14 (6.5%)	6 (4.0%)
31-40	93 (7.6%)	47 (6.5%)	21 (9.8%)	6 (4.0%)
41-50	217 (17.8%)	134 (18.4%)	42 (19.6%)	21 (14.1%)
51-60	303 (24.9%)	188 (25.9%)	48 (22.4%)	35 (23.5%)
61-70	250 (20.5%)	155 (21.3%)	46 (21.5%)	24 (16.1%)
71-80	190 (15.6%)	112 (15.4%)	20 (9.3%)	39 (26.2%)
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 (68.0%)	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 (85.0%)	184 (86.0%)	114 (76.5%)
Age 75 or older	203 (16.7%)	121 (16.6%)	33 (15.4%)	36 (24.2%)
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 (4.0%)

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: CONTROL CSR Table 8

The medical conditions reported by verified users at baseline are generally consistent with similarly aged women in the general population with about 29% taking medications for underlying medical conditions (Table 16)

Table 16 CONTROL: Baseline Medical Conditions Reported by Verified Users

	N (% in 727 Verified Users)
Osteoporosis	207 (28.5%)
Heart Disease	282 (38.8%)
Hormone Replacement Therapy	78 (10.7%)
Gastroesophageal Reflux Disease (GERD)	154 (21.2%)
Parkinson's Disease	4 (0.6%)
Depression, anxiety, other mood disorders	187 (25.7%)
Arthritis, muscle or joint pain	226 (31.1%)
Diabetes	79 (10.9%)
Breathing problems, asthma, COPD, pneumonia	94 (12.9%)
Taking medications for any other medical conditions	208 (28.6%)
Source: CONTROL CSR Table 10	

6.7.3 Effectiveness of Oxytrol OTC Label

6.7.3.1 Findings from Analysis of Primary Endpoint

Of the 727 verified users, 141 subjects developed a new symptom where the label directs them to stop use or talk to a doctor or experienced a worsening of their OAB. Of these 141, 105 continued using Oxytrol. These 105 subjects (14.4%) had potential misuse of Oxytrol based upon the initial classification from review of the closed ended responses on the CRF (Table 17). These subjects were then carefully reviewed to determine if they, in fact, had behavior that would not be appropriate in an OTC setting per the primary endpoint.

Table 17 CONTROL: Correct and Incorrect Use in Verified Users based upon Initial Classification (N=727)

Correct Use	622 (85.6%)
Subjects with no new symptoms or OAB did not worsen	586 (80.6%)
Subjects who stopped use according to label	36 (5.0%)
Developed a new symptom only	28
OAB symptoms worsened	4
New Symptom and Worsened	4
Subjects continued use but had a new symptom or worsening in OAB symptoms (Incorrect Use for Initial CRF Classification)	105 (14.4%)
Developed a new symptom only	73
OAB symptoms worsened	22
New Symptom and Worsened	10
Source: CONTROL CSR Table 13	

The review panel reviewed all CRF data including responses to open-ended questions for all 105 verified users who continued use of Oxytrol after reporting a new symptom or worsening of OAB. Of the 105 subjects, 80 had data demonstrating that the decision to continue Oxytrol was clinically appropriate. These 80 subjects were determined to have correct use in the final analysis resulting in 96.6% of subjects with correct use with only 3.4% having incorrect use (Table 18). Thus, the primary endpoint was met, demonstrating that women can appropriately deselect or stop use of Oxytrol.

A listing of these 80 subjects and reasons for mitigation are provided in Appendix 6. Of the 80 subjects who had medically appropriate reasons for continued Oxytrol, 20 talked with physicians and were told to continue, 17 stopped use when symptoms worsened, 15 talked with physicians and stopped use, and 12 had self-limited symptoms (Table 18).

Table 18 CONTROL: Summary of the Medically Appropriate Reasons to Continue Oxytrol

Total number programmatically classified as incorrect	105
Total Considered Correct Post Mitigation	80
Talked to Dr/HCP and told to continue use	20
Stopped use when symptoms worsened/became severe	17
Talked to Dr/HCP and stopped use	15
Symptom self-limited and resolved	12
Symptom/worsening OAB occurred after stopping use	10
Symptom was pre-existing (open-ended data revealed that it was misreported as a new symptom)	6
Stopped use	6
Other	6
Not an allergic reaction	2
History of worsening OAB symptoms followed by improvement	1
Source: CONTROL CSR (also cited in Appendix 6)	

Findings from analyses of the incorrect use rate based upon the initial classification and the final analysis are shown in Table 19. Based upon the initial classification of questionnaire data using only the closed in query responses, the upper CI was greater than 5%. However, careful review of all subject data shows that most of the behaviors were medically appropriate. Thus, the final analyzed data better represents this objective of the study. Based upon the final analyzed data, 3.4% of verified users failed to stop Oxytrol when they should have based upon the label (95% CI; 2.2, 5.0) meeting the definition of success.

Table 19 CONTROL: Primary Endpoint - The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Worsened Including Abdominal and/or Pelvic Pain – Users

Primary Endpoint	Initial Classification (N=727)[a]	Final Classification (N=727)
Total subjects who had no new symptoms indicating they should stop use	586 (80.6%)	586 (80.6%)
Total subjects who had symptoms indicating they should stop use	141 (19.4%)	141 (19.4%)
Total subjects who failed to stop use:	105 (14.4%)	25 (3.4%)
Developed a new symptom only	73 (10.0%)	13 (1.8%)
Condition worsened only	22 (3.0%)	11 (1.5%)
Developed new symptom and condition worsened	10 (1.4%)	1 (0.1%)
Total subjects who failed to stop use	105 (14.4%)	25 (3.4%)
95% CI (LL, UL)[b]	(12.0%, 17.2%)	(2.2%, 5.0%)

Abbreviations: CI = confidence interval, LL = lower limit, SAS = statistical analysis system.

a: Includes N=12 subjects presenting with complaints of abdominal or pelvic pain only (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences.

b: Confidence intervals derived using SAS Frequency Procedure with the Binomial option.

6.7.3.2 Sensitivity/Subpopulation Analyses of Primary Endpoint

A series of sensitivity analyses were conducted to assess the robustness of the findings for the primary endpoint as follows:

1. All 785 users - combining verified and non-verified users
2. Exclusion of subjects who reported on their diary more than 1.25 fold more patch applications than were purchased.
3. Comparison of findings in subjects (verified users) enrolled before 14 Jul 2010 (N=127) to those enrolled after 14Jul 2010 (N=600). (Study design elements were changed including information subject was provided before making purchase decision and the cost of the product).
4. Comparison of subpopulations including low literate subjects. Subjects over 65 years of age, and non-white subjects.

Results for all sensitivity analyses were generally similar to those for the primary analysis.

6.7.4 Analysis of Secondary Endpoints

6.7.4.1 Secondary Endpoint 1 (SE1)

Secondary endpoint 1, which is similar to the primary endpoint, was the proportion of verified users who did not stop use when their condition worsened or they developed a new symptom where the label directed them to stop use or talk to a doctor. The difference with the primary endpoint is that secondary endpoint 1 did not include abdominal or pelvic pain as a reason to discontinue use of Oxytrol. Secondary endpoint 2 included the mitigation results for primary endpoint 1 except for subjects who reported only abdominal or pelvic pain.

Based on the pre-mitigation algorithm, 86.9% met secondary endpoint 1. Following adjudication by the mitigation panel, 96.8% met secondary endpoint, above the pre-defined rate. The upper CI is 4.7%. The addition of abdominal or pelvic pain had no significant impact on the results of the Primary Endpoint vs. Secondary Endpoint 1.

Full results for Secondary Endpoint 1 are found in Appendix 7.

6.7.4.2 Secondary Endpoint 2 (SE2)

Secondary endpoint 2 is the median time taken to discontinue Oxytrol use by verified users who did not experience improvement in their OAB symptoms after two weeks of treatment. Of the 643 subjects who stated that they used Oxytrol for 2 weeks, 456 (70.9%) reported an improvement in their OAB symptoms and 187 (29.1%) subjects reported no improvement in their symptoms. In these 187 subjects, the median time to discontinue (endpoint #2) was 35 days. However, for users who reported an actual worsening of their OAB symptoms, the median time taken to discontinue use of Oxytrol was only 8.5 days.

Of the users who did not report an improvement in their OAB symptoms, the 10 users who continued to use Oxytrol despite worsening symptoms were carefully reviewed. In CONTROL, 10 users reported a worsening of their OAB and applied another patch after the onset of the worsening. Six of these subjects were determined to have medically acceptable behavior based on mitigating factors. Three subjects spoke to their doctor and one subject reported intermittent worsening at week 3 followed by improvement at the other visits. One subject stopped using Oxytrol and resumed her prescription therapy. Four users were not mitigated. Three had previously been diagnosed with OAB and had been taking a prescription product for OAB before enrolling in CONTROL. These users were not mitigated because they continued using Oxytrol without talking to their doctors. It is possible that they did this because they knew they had OAB and were not putting themselves at risk. They all experienced an improvement after resuming their previous treatment.

6.7.4.3 Secondary Endpoint 3 (SE3)

Secondary endpoint 3 was the proportion of verified users who did not stop Oxytrol use within two weeks after experiencing no improvement in their OAB symptoms (OAB rated as worsened or stayed the same). Secondary endpoint 3 was analyzed using the mitigation process. The initial program identified all users who, according to their close-ended data at their first follow-up interview, reported that they continued to use the patch beyond two weeks, even if for only one day, without experiencing improvement. Two MCC clinical researchers, with oversight by an MCC clinical physician, reviewed these data to see if there were mitigating factors in the users' open-ended data that demonstrated their behavior was acceptable and correct.

88.9% of users met this endpoint. 71% of users experienced an improvement in their OAB symptoms within two weeks, and 18% correctly stopped using the product when they experienced no improvement. 11% of users did not report symptom improvement in two weeks but continued to use Oxytrol. Reasons subjects gave for continuing use included: symptoms did improve or wanted to give the drug longer to work.

6.7.4.4 Secondary Endpoint 4 (SE4)

Secondary endpoint 4 explored the medical risk associated with the development of new symptoms or when OAB symptoms did not improve for users who continued Oxytrol treatment. These medical risk categories were predefined in the protocol and are displayed in Table 20.

Table 20 CONTROL: Medical Risk Classification for Incorrect Use for Secondary Endpoint 4

Risk Level	Conditions/Symptoms
Medical risk	Narrow-angle glaucoma Were pregnant or breast-feeding Allergic reaction to the product or any of its ingredients Flank or back pain with fever Pain or burning when urinating (with or without fever or chills) but without flank or back pain Blood in the urine Urine that is cloudy or foul-smelling
Possible medical risk	OAB symptoms worsened significantly with abnormal urinalysis Unable to empty bladder completely (urinary retention) Lower back or side pain without fever Diagnosed with gastric retention (or stomach that empties slowly) Diagnosed with liver or kidney disease Unexplained weight loss Begins using a diuretic
Minimal/insignificant medical risk	OAB Symptoms Stayed the Same (relative to last visit) OAB symptoms worsened significantly with normal urinalysis
Source: CONTROL protocol	

Minimal risk includes women who reported that their symptoms either stayed the same or worsened at weeks 3, 7, and 12 but who had a normal end of study urinalysis. Including subjects who reported that their OAB symptoms stayed the same at visits 7 and 12 makes the minimal risk assessment very conservative since users were asked to rate their symptoms compared to their last visit rather than against baseline. Users may have said their OAB symptoms stayed the same at weeks 7 or 12 in relation to the last visit, but they may have previously experienced an improvement. Furthermore, the intensity of OAB is variable.

Since the mitigation process for the primary endpoint evaluated whether or not subjects displayed medically appropriate behavior for all new symptoms they experienced rather than by individual symptoms, secondary endpoint 4 was not analyzed using subject behavior data that had been mitigated.

95% of the women in the study experienced no risk or minimal risk. Of the 39.1% of the subjects in the study who experienced minimal risk, 90% never experienced a worsening of OAB symptoms. They reported that their OAB stayed the same at weeks 3, 7, or 12.

Symptoms were classified as a medical risk in 2.2% (16) of subjects (Table 21). The most common symptoms reported that were classified as consistent with medical risk were "allergic reaction to the product or any of its ingredients" (9 subjects or 1.2%) and "pain or burning when urinating (with or without fever or chills) but without flank or back pain" (6 subjects or 0.8%). One subject (0.1%) reported urine that was cloudy or foul smelling.

Regarding the allergic reactions reported by 9 subjects, true systemic reactions to Oxytrol are rare and since subjects were not seen by a study investigator and reported their symptoms on the telephone, these reported events may have more appropriately been skin irritation resulting from the drug or the adhesive. Data collection by telephone in this study was such that any subject who used the word allergy to describe an AE was recorded as an allergic reaction. Of the subjects who experienced pain and burning, 5 of the 6 were mitigated for the primary endpoint. The subject with cloudy urine also stated she had cloudy urine during her enrollment interview and had discussed it with her doctor along with other eligibility criteria and her doctor told her it was okay for her to use the patch.

Twenty-four subjects (3.3%) reported symptoms categorized as a possible medical risk, with the most common symptoms being "OAB symptoms worsened with abnormal urinalysis" (urinalysis result not negative and not missing); (1.7%) and "lower back or side pain without fever" (1.1%). Clinical review of these events was reassuring. None of the 12 patients with "urinalysis result not negative and not missing" had any evidence of UTI during the study and all 8 patients with lower back or flank pain had history of injury and no other urinary symptoms.

Table 21 Medical Risk Classification

Secondary Endpoint 4	All Subjects (N=727)[a]
Medical risk (subjects)	16 (2.2%)
Symptoms	
Narrow-angle glaucoma	0 (0.0%)
Are pregnant or breast-feeding	0 (0.0%)
Allergic reaction to the product or any of its ingredients	9 (1.2%)
Flank or back pain with fever	0 (0.0%)
Pain or burning when urinating (with or without fever or chills) but without flank or back pain	6 (0.8%)
Blood in the urine	0 (0.0%)
Urine that is cloudy or foul-smelling	1 (0.1%)
Possible medical risk (subjects)	24 (3.3%)
Symptoms	
OAB symptoms worsened with abnormal urinalysis (urinalysis result not negative and not missing)	12 (1.7%)
OAB symptoms worsened with no urinalysis conducted	0 (0.0%)
Unable to empty bladder completely (urinary retention)	4 (0.6%)
Lower back or side pain without fever	8 (1.1%)
Diagnosed with gastric retention (or stomach that empties slowly)	0 (0.0%)
Diagnosed with liver or kidney disease	1 (0.1%)
Unexplained weight loss	0 (0.0%)
Begins using a diuretic	0 (0.0%)
Minimal/insignificant medical risk (subjects)	284 (39.1%)
Symptoms	
3-week interview	
Condition stayed the same	137 (18.8%)
Condition worsened	7 (1.0%)
7-week interview[a]	
Condition stayed the same	142 (19.5%)
Condition worsened	13 (1.8%)
12-week interview	
Condition stayed the same	151 (20.8%)
Condition worsened	10 (1.4%)
OAB symptoms worsened with normal urinalysis	1 (0.1%)

[a] Subject assessment of OAB symptoms at the 7-week and 12-week interviews asked subjects to evaluate their symptoms relative to last follow-up interview.

Note: Subjects are only counted once in each medical risk category even though they may have reported more than one symptom

Source: CONTROL CSR Table 27

6.7.4.5 Secondary Endpoint 5

Secondary endpoint 5 was the proportion of verified users who misused the patch (incorrect duration of use > 4 days or simultaneous use). Subjects who had a single patch use greater than four days or a single overlap of patch use were identified as possible misusers for this endpoint. Of the users in CONTROL, 21.6% reported incorrect use of the patch. Of these subjects, most wore one or more patches for longer than 4 days.

3.1% (N=22) of subjects reported use of more than one patch at a time. Of the 22 users with simultaneous patch use, 4 experienced a mild irritation at application site. Most of the simultaneous misuse appears to be diary card errors and many of these subjects denied wearing more than one patch at a time when asked about it.

6.7.4.6 Combined Primary Endpoint/Secondary Endpoint 3

This shows the proportion of subjects who did not stop use when they either developed a new symptom where the label indicates they should stop use or talk with their doctor or when their OAB symptoms did not improve with the addition of abdominal or pelvic pain. This combined analysis was conducted using both pre- and post-mitigated data is shown in Appendix 7.

In the user population of 727 subjects, the total number of subjects who continued using Oxytrol when they developed a new symptom where the label indicates they should stop use or talk with their doctor was 89 (12.2%) using post-mitigated data. Therefore, 87.8% of subjects demonstrated acceptable ongoing use behaviors per the combined primary endpoint and secondary endpoint 3.

6.7.5 Ongoing Use by Subjects who Developed Safety Issues of Special Interest

6.7.5.1 Subjects who Developed Symptoms Associated with a UTI

The Oxytrol label was designed to educate women that while urinary frequency is a symptom of OAB, it could also be a symptom of a UTI. Per the label, women are instructed to see their doctor if they are experiencing pain or burning while urinating, blood in urine, lower back or side pain, or urine that is cloudy or foul-smelling.

Of the 26 users who developed symptoms associated with UTI (pain or burning when urinating, fever, chills, blood in urine, flank or lower back pain, urine that is cloudy or foul-smelling) while using the patch, 24 demonstrated acceptable medical behavior per the primary endpoint as discussed above. Of the other two, one had cloudy urine but continued treatment. Her symptoms resolved without treatment and she had a negative urinalysis at the end of the study pharmacy visit. The other woman developed a UTI that she did not recognize, which was diagnosed at the end of study urinalysis. She sought treatment and her UTI resolved.

Despite the emergence of new symptoms associated with UTI in these 26 subjects, most of their OAB symptoms either improved or stayed the same. Only 2/26 (7.7%) subjects reported that their OAB symptoms worsened during use. Neither of these subjects (SN 14-0022, SN 27-0069) was diagnosed with UTI during use or through the end-of-study UA. SN 14-0022 stopped using the patch because of her pain or burning when urinating and worsening urge incontinence, and symptoms resolved by end of study. Subject 27-0069 drank cranberry juice while continuing to use the patch, and her symptoms of worsening urge incontinence and pain or burning when urinating improved after 1-2 days.

6.7.5.2 Subjects Diagnosed with UTI or Bladder Infection

Separately, 27 women reported a UTI at one of the follow-up interviews. All of these subjects exhibited acceptable behavior. They either recognized their symptoms and sought treatment or were diagnosed with the UTI through health care they received outside of the study. Using Oxytrol for urinary frequency did not prevent these women's diagnosis of UTIs.

In addition to these 27 UTIs, there were 34 other UTIs or bladder infections that were reported as adverse experiences which occurred outside of the use period and were not evaluated for ongoing use behavior. Fifteen of these subjects recognized symptoms or were treated through routine care outside the conduct of the study. With the exception of the one user who had symptoms of UTI she did not recognize (this is the same subject mentioned earlier in Section 6.7.5.1), all of the users diagnosed with UTI were either asymptomatic, which current treatment guidelines specify would not be treated or developed symptoms after stopping the use of Oxytrol.

6.7.5.3 Subjects who Developed Symptoms of Diabetes

No subject who used the patch reported symptoms of frequent urination with excessive thirst, extreme hunger, or increased tiredness during their follow-up interviews. However, one subject was diagnosed with diabetes during the study. Subject 12-0121 reported at follow-up Week 3 that she had been diagnosed with diabetes by her doctor and was instructed to stop using the patch. This subject reported during the enrollment interview that she had experienced frequent urination with excessive thirst, extreme hunger, or increased tiredness. It does not appear as though the use of the patch delayed her diagnosis of diabetes. She also reported that she had urinary frequency, urgency and incontinence for 5 years. It is unclear if she had an existing appointment with her doctor or made an appointment after reading the label. This subject reported an improvement in her OAB after use of Oxytrol at her follow-up week 3 interview. At the end of study interview the subject reported that her doctor told her it was okay for her to use the patch but that she did not have money to continue purchasing the patch.

6.7.5.4 Symptoms that could Indicate Allergic Reaction to Oxytrol

Allergic reactions in CONTROL were collected over the telephone. If the subject mentioned the word "allergy," it was recorded as an allergic reaction. It is possible that these women were having skin reactions rather than true allergic reactions to Oxybutynin, which are rare and usually are characterized as hives, difficulty breathing, and swelling of the face, lips, tongue, and throat. Of the 16 subjects who self-reported symptoms indicative of an allergic reaction, 12 subjects (75.0%) stopped using the patch (10 stopped without talking to a doctor and 2 stopped after talking to a doctor). By the follow-up Week 12 telephone interview, only four subjects continued to use the patch without talking to a doctor. Based on an in-depth review of case report form data, three of the four subjects who continued use may have experienced an allergic reaction. All of these reactions were of mild intensity and affected the skin in areas other than the patch application site.

6.7.5.5 Subjects with Symptoms of Potential Ineligibility at Baseline

This study was not intended or designed to rigorously collect self-selection information. Although a purchase decision question was asked, the self-assessment question (Is this product right for you?), was not asked. In this naturalistic study, subjects who did not strictly meet all of the ineligibility criteria on the Drug Facts label were allowed to purchase Oxytrol. This enabled observation of use patterns and safety in subjects who might potentially use the product despite not meeting every label criterion as it was asked during the eligibility assessment.

Although this study was not designed as a self-selection study, this section analyzes subjects' purchase decision responses. It is important to understand that the eligibility assessment questionnaire appeared to be very sensitive and women responded yes to questions when they may not have actually had the condition. For example, 42.8% of evaluators responded that they had a "feeling that they can't empty bladder completely." This question was meant as a surrogate for the label's warning for urinary retention, which states "Do not use if you have urinary retention (are not able to empty your bladder). Although there were seven urinary retention AEs in CONTROL, none were acute and this high proportion of women reporting "feeling they can't empty bladder completely," is an example of why the responses to subject history questions are difficult to interpret.

Possible ineligibility criteria reported by purchasers included foul-smelling urine (9.6%), cloudy urine (7.0%), and pain or burning when urinating (3.8%). To interpret the significance of the reported symptoms, each symptom was classified into medical risk using the same criteria and method as used for Secondary Endpoint #4. Of the 1220 subjects, 209 (17.1%) reported a symptom that was characterized as being of potential medical risk (Table 22). Some of these subjects were excluded at enrollment and are discussed in Section 6.7.2.2. Most of the other symptoms are related to UTI. Of these subjects that had symptoms of UTI at enrollment, the majority reported an improvement in their OAB symptoms at Week 3 (69.5%). This

is similar to the improvement reported at Week 3 in the general population. Eight of these subjects did develop UTIs during the study. Seven of these subjects recognized that they had symptoms of UTI during use or received treatment through routine care. One subject did not recognize her symptoms of UTI and continued to have UTI symptoms throughout the study. She was only diagnosed through the End of Study urinalysis. This same subject has been mentioned in every section regarding UTI.

Table 22 Ineligible Symptoms at Baseline of Potential Medical Risk

Ineligibility Criteria	**Evaluators (N=1220)**
Total Subjects with Ineligible Symptoms	209
Narrow-angle glaucoma	4 (0.3%)
Pregnant or think you might be pregnant	0
Allergic to oxybutynin	5 (0.4%)
Lower back or side pain with fever	4 (0.3%)
Pain or burning when urinating (with or without fever or chills)	53 (4.3%)
Blood in the urine	15 (1.2%)
Cloudy urine	91 (7.5%)
Foul-smelling urine	116 (9.5%)
Are breastfeeding	5 (0.4%)
Source: CONTROL CSR	

6.7.5.6 Subjects Who Did Not have 2 or More OAB Symptoms for more than 3 Months

The Oxytrol label states that a consumer should have 2 or more symptoms of OAB for at least 3 months to use Oxytrol in order to reduce the chance that the reported OAB symptoms could be due to an emerging UTI unrelated to OAB or to undiagnosed pregnancy. Of the 785 subjects who reported use of Oxytrol, 88 did not have two or more OAB symptoms (urinary urgency, urinary frequency, and urinary incontinence) for more than 3 months. Careful review of the subject data in these 88 did not find any evidence of a delay in diagnosis of a potentially more serious condition. Only 7 symptoms were reported by 6 subjects during use in these 88 subjects.

The abdominal pain, reported by SN 28-0111 as abdominal pain at application site, was not associated with a UTI. Subject 35-0033 reported lower back pain with no associated symptoms or diagnosis of UTI. Subject 10-0051 reported a bladder infection that developed more than 5 weeks after the first patch application date. Subject 37-0140 developed pain or burning when urinating and UTI 3 weeks after first patch application date (this subject discontinued patch use ~ 1 month before

development of UTI). The other two reports of UTI were 7 and 8 weeks after first patch application date. In summary, based on the nature and timing of onset of the noted symptoms in these 6 subjects, there is no evidence that the subjects confused their OAB symptoms at enrollment with those of an underlying UTI.

6.7.6 Conclusions from CONTROL

The ongoing use and safety of Oxytrol in an OTC setting has been carefully assessed in a simulated naturalistic setting. The results of the study demonstrate that in an OTC market setting:

- The Oxytrol Drug Facts label will drive appropriate ongoing use decisions.
- A small group of women who use Oxytrol may develop a worsening of their OAB symptoms or develop new symptoms that indicate they should stop use.
- Women using Oxytrol will be able to appropriately recognize new symptoms of relevant medical risk and will seek treatment.
- Oxytrol can be safely used by women to treat symptoms of OAB without the need for physician diagnosis or prescription.
- The adverse experiences reported by subjects using the Oxytrol patch in the CONTROL study were consistent with those observed in the original NDA studies and in post-marketing experience.

6.7.7 Final Proposed Drug Facts for Oxytrol for Women

Several minor changes were made to the label after it was studied in Stage II label comprehension, self-selection and CONTROL, including the following:

- Urinary retention has been clarified in two areas: 1) "You are not able to empty your bladder (urinary retention)" was added to the "Stop use and ask a doctor if" subheading, and 2) in the "Do not use" subheading, a statement referring to doctor diagnosis was added to urinary retention [“Do not use if you have been told by a doctor you have urinary retention (are not able to empty your bladder”)].
- The highlighted warning about undiagnosed pregnancy, UTI, and diabetes was changed from sentences to a bulleted format to enhance readability.
- The UTI-related symptoms in the "Do not use" subheading were regrouped to better associate them with UTI and enhance their readability.
- The diabetes-related factors and symptoms in the "Ask a doctor before use if you have" subheading were reformatted to better associate them with undiagnosed diabetes.

The proposed Drug Facts labeling text is detailed below:

Drug Facts

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

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 <u>any</u> 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

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 redness 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.

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

7.0 BLADDER HEALTH EDUCATION AND SUPPORT PROGRAMS

Consumer education is an important component of any switch program. Education helps to increase awareness and enhances a consumer's ability to effectively self-recognize and self-manage a condition.

Overactive bladder is a condition that is largely self-managed by women today due to a lack of knowledge that OAB is a treatable medical condition and because women are simply uncomfortable discussing this embarrassing condition with their healthcare provider. Despite the significant impact this condition has on their quality of life, most women choose to manage the condition solely with absorbent products and/or significant lifestyle alterations, while just 20% use a pharmacological product to help manage their condition. Women need access to better self-management tools to help improve their quality of life as well as better information to help guide appropriate behavior in managing this condition.

The OTC availability of Oxytrol will boost accessibility to more effective self-management of OAB, and will help to de-stigmatize this condition for millions of women.

7.1 Educational Plans Based on Extensive Research

The education and support program designed for Oxytrol was developed based on educational gaps that exist today, not just for OAB, but for urinary health in general. These gaps were identified through:

- Discussions with, and input from, numerous professional and consumer organizations
- Advice and guidance from a multi-disciplinary board of healthcare providers (urologists, family practitioners, gynecologists, uro-gynecologists, uro-oncologists, endocrinologists, geriatric urologist, dermatologist, nurse practitioner specializing in urology) established by MCC to advise and guide us relative to the appropriate development plans for Oxytrol as an OTC product.
- Extensive consumer research including a comprehensive literature review and quantitative research, as well as hundreds of detailed one-on-one interviews with women in order to gain an in-depth understanding of how they feel about their OAB condition; how they currently choose to manage it; and the impact it has had on their lives.
- A linguistics study to understand how both consumers and professionals talk about OAB, and how to use language to help open up the lines of effective communication

In order to establish a measurable baseline of current consumer beliefs and behaviors prior to the initiation of the Oxytrol educational plan, an Attitudes and Usage study (A&U) was fielded in July 2012 among 814 females between the ages of 18-75 who had experienced OAB in the past 12 months (Forbes OAB Study 2012). Study sample was weighted to age, ethnicity and Rx usage to be representative of women with OAB.

Key findings from the A&U study helped to shape the direction of the educational messaging. Some major findings are as follows:

- Most women are using self-management strategies to help them cope with their OAB condition, including 51% using solely absorbent pads. Just 20% use a prescription product to treat their OAB.
- Early OAB symptoms tend to go untreated or are managed with panti-liners only. As symptoms progress, women resort to heavier protection products.
- Women tend to wait an average of 6.5 years before deciding to discuss their OAB with their healthcare provider. When asked why they waited so long, some of the leading answers included "I thought it was just a normal part of getting older" (40%), "I'm embarrassed/uncomfortable to talk about it" (29%), "My doctor never asked me if I had a bladder control problem" (27%) and "I didn’t think anything could be done about it" (21%).

7.2 Oxytrol for Women: Educational Goals

Based on all of these collective findings, the goals for the Oxytrol educational program are as follows:

- Increase awareness that overactive bladder is a treatable medical condition and not a normal part of aging.
- Educating women about other potential causes of urinary frequency, information that is currently not readily available on either the prescription or OTC side.
- Ensure that both behavioral and pharmacological treatment options are communicated so that women will feel empowered to take control of their OAB.
- Reduce the current barriers that are preventing women from having conversations with their healthcare providers

7.3 MCC Commitment to Deliver These Goals

MCC will accomplish these goals through the well-tested Drug Facts label, a broad array of unbranded educational initiatives with prominent organizations, and a broad, multi-faceted outreach to ensure that the impact of our messaging is heard and understood by all stakeholders, including those of lower literacy, non-English speakers, and those in typically under-served communities.

7.3.1 The Label

The most basic educational component of this program is the label. The Oxytrol label addresses the concern about the potential delay in diagnosis of other conditions. It provides specific information about other conditions which may have urinary symptoms, an important communication point that is currently not being delivered on either prescription labeling or on OTC paper products.

In addition to the label itself, the website will have the label available in Spanish and will also contain audio directions for use with detailed graphics clearly depicted for the low literate consumer.

7.3.2 Unbranded, Educational Programs

MCC has collaborated with several prominent organizations to develop non-branded, educational programs to address the program goals established for Oxytrol. MCC has firm commitments in place and are in the process of developing non-branded educational programs with the following organizations:

- American Urogynecologic Society
- Nurse Practitioner's in Women's Health
- National Association for Continence (NAFC)
- Simon Foundation for Continence
- Alliance for Aging Research
- Society for Women's Health Research
- Healthy Women
- Business and Professional Women's Foundation

These pre-launch unbranded, multi-lingual programs will include in-office and online brochures and quizzes, educational articles and fact sheets both in print and online, a media press event for healthcare publications, as well as custom research studies which will be published to further enlighten women and healthcare providers about this condition. Many of these organizations will display the materials MCC has helped to develop and the results of research MCC has collaborated with them on at Bladder Health Week, a week-long awareness campaign coordinated by NAFC to encourage individuals to talk to their friends, loved ones and healthcare providers about bladder health, and OAB in particular.

7.3.3 Post-Approval Educational Initiatives

Marketing programs to support OTC availability of Oxytrol are also expected to promote greater awareness of urinary system health awareness and monitoring. People who would otherwise ignore the problem until it reaches significance would be educated about the importance of seeking care to avoid the risk of more serious medical conditions that may mimic or be linked to overactive bladder. In the OTC setting and through a broad multidisciplinary educational effort that will accompany the marketing of this product, women with OAB will have an opportunity to gain valuable knowledge regarding their condition and available treatment options. They will also gain an awareness of the importance of seeing a physician, when appropriate, to evaluate and monitor their overall urinary health, especially in conjunction with distinct symptoms of other more serious conditions that could potentially overlap with those of OAB. Likewise, the medical community will be encouraged to raise the status of OAB and promote an open dialogue with their female patients about OAB and urinary health as well as invited to step into a broader leadership role.

These educational initiatives to increase awareness of OAB as a treatable medical condition, and educating consumers about overall urinary system health, will also be supported by the following specific post-approval marketing efforts:

- MCC will initiate contact with additional medical and disease organizations to encourage a broader but more focused range of activities by these groups.
- Comprehensive point-of-purchase educational effort with pharmacists to ensure these front-line healthcare providers have the resources they need to appropriately guide their consumers.
- Supported post-OTC launch with educational consumer advertising, an interactive website and a public relations campaign featuring spokespeople women can relate to.
- Announcements and articles in membership publications, websites, newsletters and other communications mechanisms about this new ‘first-in class' OTC OAB agent.
- Social media outreach.
- National and regional conference workshops.
- Hosting OAB and continence leaders as speakers at national conferences and local chapter meetings.
- Development and dissemination of collateral materials.
- Web-based education.

A balanced and responsible marketing program will be put into place that will surround the OAB consumer with educational messaging that will reach them from numerous venues including print, TV, public relations, and an educational, interactive website that will encourage discussion among consumers and professionals, as well as mailings to all pertinent health care professionals (i.e. physicians, pharmacists, nurses, nurse practitioners, health clinics, etc.) informing them of the OTC availability of Oxytrol and providing them with educational materials to share with their patient population.

7.3.4 Behavioral Education will be Critical

An important component of all of these pre- and post-launch initiatives will be a total support program to provide women with an integrated personalized program to help them effectively manage their OAB. This will include behavioral modification strategies, online interactive support tools and pharmacological options all designed to work synergistically to improve overall outcomes, very similar to other OTC lifestyle management categories such as weight loss or nicotine replacement patches.

Behavioral strategies that will be encouraged are as follows:

- Kegel exercises
- Fluid management
- Lowering caffeine/alcohol Intake
- Diet modification
- Timed bathroom visits

Finally, a crucial element of the education and support program is that it will be measured and modified as appropriate on an ongoing basis.

Attitudes and behaviors will be surveyed at regular intervals against the July 2012 baseline research. Key measures will be changes from baseline that directly relate to the overall goals of the program, such as changing the belief that OAB is a normal part of aging, and increasing awareness that there are effective steps towards managing this condition and their overall urinary health. This ongoing research will help to serve as a compass to evaluate our program and the impact it has had on women with OAB and re-direct efforts if necessary.

The OTC availability of Oxytrol combined with a rich educational program has the ability to improve quality of life for millions of women with OAB. OTC availability will empower women to take back control of their lives by providing convenient, open access to an effective medication. Education and awareness will help to de-stigmatize the condition so women will realize that this is not a normal part of aging

and this may help to encourage open, honest conversations between women and their healthcare providers about their overall bladder health.

8.0 BENEFIT RISK ASSESSMENT OF NONPRESCRIPTION OXYTROL

OAB is an appropriate condition for OTC self-care and the oxybutynin TDS is especially suited for nonprescription status to treat the symptoms of this condition. It has a strong safety profile and clinically meaningful efficacy for women with OAB. More convenient access to the medication would also represent an improvement in the current paradigm for the substantial portion of women who self-manage their symptoms by disrupting or altering their lifestyles to cope with or conceal their urinary symptoms. The well-studied Oxytrol Drug Facts label demonstrates that consumers can appropriately self-select and, subsequently, de-select to stop use in the OTC setting without the intervention of a health care professional. For the small percentage of women who might continue to use inappropriately in the OTC setting, the attendant risks would be small and no greater than what currently exists for the large number of women who already self-manage OAB without a pharmacologic option.

OTC treatment of OAB symptoms is consistent with other OTC switch paradigms. Conditions like allergy and frequent heartburn are chronic but intermittent and of varying intensity and individual perceptions. OTC medicines help reduce symptoms and allow people to experience an improved quality of life and participate in regular daily lifestyle activities.

8.1 Safety and Efficacy of the Oxytrol TDS

Over the past 30 years, transdermal drug delivery has become a proven technology that offers safety and convenience benefits over oral dosage forms. By delivering drug directly into systemic circulation via skin application and bypassing first-pass gastric and hepatic metabolism, transdermal agents are able to improve tolerability, promote better adherence, and avoid peaks and troughs seen with oral agents as they reach therapeutic concentration. The patch, however, does cause skin irritation in some users which can be minimized by changing the site of application from dose to dose. Transdermal patches are widely available in other OTC products and the skin irritation some users experience with oxybutynin TDS should not preclude consideration for wider access without a prescription.

Clinical trials have demonstrated the efficacy of oxybutynin TDS in the treatment of OAB and supported FDA approval for the prescription product. Oxybutynin TDS treatment reduces the number of daily incontinence episodes and daily urinary frequency, and increases the average daily urinary volume per void, with a lower risk of anticholinergic side effects such as dry mouth and constipation compared to oral oxybutynin. The efficacy, although moderate and not experienced by all patients in clinical trials, is similar to that seen with oral anticholinergics and those who do respond experience clinically meaningful symptom relief. Oxybutynin TDS treatment also leads to improvements in quality of life measures, including social relationships, travel, emotional health, sleep/energy, physical activity, irritative symptoms, sexual function, and work productivity.

Thus, when considering the proposal to expand access without a prescription, the overall safety and efficacy of Oxytrol should not be in question. Rather, the determination should focus upon whether or not women can self-recognize the condition and appropriately use or stop using the product over time.

8.2 Self-Management of OAB is the Norm

The majority of women with OAB have already been told by a doctor that they have the condition or recognize they have its symptoms. Most of these women employ a range of self-management approaches and life-style modifications in order to cope with this debilitating, chronic condition or conceal its symptoms. This is despite the fact that a range of prescription medications and behavioral strategies are available. In fact, only 20% of women with OAB currently use a prescription medication to manage their condition. The majority relies on absorbent products (51%). (Gallup OAB Study 2011, Forbes OAB Study 2012).

The reason that self-management is the norm for this condition involves a number of factors. Many women who experience OAB believe that it is a normal consequence of growing older, having never been informed by their practitioners that there are effective medications available (Muller 2010). Furthermore, many are too embarrassed to initiate a discussion with their doctor (Forbes OAB Study 2012). And, despite the effects of OAB on life and lifestyle, data demonstrate that the OAB sufferer is often reluctant to initiate a conversation about this condition with a physician, even though she visits a doctor's office an average of 6.9 times per year for other reasons (Harris Interactive 2003). In fact, a substantial proportion of women with OAB (24-34%) never address their urinary concerns with their doctors. Those who do, wait an average of 6.5 years before reaching out for medical advice (Gallup OAB Study 2011), often driven by frustration over coping with symptoms (Muller, 2010) and increasing symptom severity (Irwin 2008).

Overwhelmingly (91% of the time), physician involvement in the issue occurs when women proactively initiate the conversation with their doctor. In those cases, women with OAB often report feeling that physicians seem to trivialize their condition (Harris Interactive 2003); do not understand the extent to which symptoms affect overall quality of life (Marschall-Kehrel 2006); and lack interest, empathy, and knowledge about OAB (Bradway 2008). A recent study showed that only 30% of women who discussed this problem with their physician felt that their problem was taken seriously (Forbes OAB Study 2012).

8.3 The Oxytrol OTC Label Paradigm Directs Behavior Intended to be Consistent with a Medical Approach

A formal medical diagnosis of OAB is often based upon exclusion of underlying diseases like urinary tract infections (UTIs), abnormal bladder pathology including bladder cancer (BC), diabetes (DM), pregnancy, and prostatic hypertrophy that can produce OAB symptoms.

The rationale that Oxytrol is appropriate for use without direct involvement of a health care professional employs the following self-management labeling safeguards:

1. The consumer labeling must successfully direct a large majority of consumers to make a correct "self-selection" decision that the product is right for them. In this case, correct self-selection includes that the consumer is a woman with symptoms consistent with OAB and without the medical conditions or situations which warn against use, such as those identified above.
2. Once using the product, the label must successfully direct a large majority of consumers when to stop use (de-select) or consult a professional because of a change in their medical status or lack of effect.
3. If the label is shown through study to be successfully guiding correct initial self-selection and subsequent correct de-selection during use, only a very small cohort of consumers will continue to use the product incorrectly. In this case, the inherent safety of the product and the natural history any non-OAB condition they might have must not lead to unacceptable risks or outcomes.

With these tenets in mind, MCC took the following approaches to developing the OTC Drug Facts label:

- The target population is limited to adult women and product graphics and labeling are clearly unambiguous in this regard. Men who have symptoms of OAB may require a prostate exam and should not use nonprescription Oxytrol without a professional recommendation.
- The label also instructs that OAB symptoms should be present for at least 3 months to reduce the risk that women will not use the product if they have more acutely emergent symptoms that may be associated with UTI or early pregnancy.
- A prominent warning in the label alerts women that other conditions may also have urinary symptoms similar to OAB. These other conditions might also cause urinary frequency and urgency (e.g., pregnancy, UTI, diabetes, and bladder cancer) such that there could be a delay in diagnosis or treatment of these other conditions. These messages are not currently communicated on absorbent products or on prescription labeling aimed at consumers and encourages conversations between women and their healthcare professionals about urinary health in general.
- The OTC label also includes a directive to seek medical care if no improvement is seen within a conservative two-week time period. While some clinicians find that a 2-week interval is adequate, others recommend 4 weeks or more.

In summary, the Oxytrol label informs women that they may have OAB if they have had symptoms for at least three months, allows for a two week use period, and provides very specific guidance on other urinary symptoms that should be evaluated by a health care professional. It must be kept in mind that most women with OAB today choose to manage this condition on their own with sub-optimal methods, such as absorbent products and self-imposed lifestyle restrictions that impact quality of life. If conversations do occur between a woman and her physician, it typically happens after having OAB for a number of years. The nonprescription availability of Oxytrol will provide an effective self-management option, help to improve quality of life and educate women about other causes of urinary frequency/urgency in an effort to encourage communication with healthcare professionals.

Thus, the OTC label:

- helps women identify potential underlying disorders that could present with frequent urination or urgency as symptoms
- directs women to evaluate their response to treatment within a short time frame,
- urges women to consult a doctor if symptoms do not improve or new symptoms of potential concern emerge

This information is not readily available to the many women who are currently managing their symptoms on their own.

8.4 The Label is Well-Studied and Performs as Intended

The consumer behavior studies reviewed in this document provide the backbone of a data-driven conclusion that the Oxytrol Drug Facts label does in fact guide the desired appropriate behavior. The results from the series of label comprehension and self-selection studies demonstrate that the label messages regarding directions for use and the key safety warnings are well understood by the broad target population and important cohorts, and that the label effectively guides self-selection among the target and subgroups.

In Label Comprehension Studies:

- Respondents demonstrated excellent comprehension of product use for treatment of OAB (96-100%) and showed strong understanding of OAB symptoms (83-91%).
- Recognition that symptoms of possible bladder cancer and urinary tract infections preclude use also achieved high scores. Blood in the urine (94%), lower back pain (91-95%), and pain when urinating (91-92%) were consistently understood.
- Males understood the message that the product is not for men (95%).

- 93% of women understood the enhanced pregnancy warning.
- A general population of OAB symptom sufferers attained a score of 93-94% on the diabetes messages and respondents with some risk for diabetes scored 88-89%.
- Older women understood the directions for use and important safety warnings with nearly all important messages achieving 80% or higher understanding.
- The lowest scoring question occurred with stress incontinence (77%), which is a benign condition for which Oxytrol will not work and therefore was a communication objective with lower medical consequence.

In summary, most key messages were effectively communicated, meeting or narrowly missing their objectives. Overall, actual scores were generally 87% and higher, with a number of important messages reaching 90% or more.

In Self-Selection Studies:

- 95% or more of respondents made a ***self-recognition*** assessment which was consistent with that of a physician or which was associated with minimal or no risk.
- 92% or more of respondents made a ***self-selection*** decision which was consistent with that of a physician or which was associated with minimal or no risk.
- 90% of men self-selected appropriately.
- 92% of pregnant women self-selected appropriately.

In the CONTROL Actual Use Study:

- The primary endpoint was met, demonstrating appropriate de-selection. Of the 727 subjects, 3.4% of verified users failed to stop using Oxytrol when they should have based upon the label, with the addition of abdominal and pelvic pain (95% CI; 2.2%, 5.0%). The findings were consistent by age, race, and literacy level.
- Additional secondary endpoints examining consumer behavior also demonstrated appropriate ongoing use decisions, although many women reported that they needed longer than the two weeks recommended to assess whether or not the product was working for them.
- 98% of women who developed a UTI during the study acted appropriately.
- The safety experience was consistent with the approved prescription product labeling and no new adverse events of concern emerged in this actual use study. Patch irritation was the most commonly reported adverse event.

Consumer Behavior Summary

The Oxytrol OTC label was tested for effectiveness in label comprehension and self-selection studies and in an actual use study. These studies affirm that the Oxytrol OTC label allows for self-selection and self-care with no serious consequences of incorrect use.

- Messages regarding the key safety warnings were well understood by the broad target population as well as important subgroups.
- Women recognized and understood OAB symptoms and that some underlying diseases could present similar symptoms.
- Women recognized that some OAB symptoms could be signs of a UTI and that if pain or dysuria were present they should see a health professional.
- The label directives regarding undiagnosed diabetes, family history of diabetes, presence of hematuria, and pregnancy were well understood by both general populations of women with OAB symptoms and specific subgroups.
- Men recognized that Oxytrol was not for males.
- In the actual use study (CONTROL), most consumers appropriately discontinued using the product based upon the recommendations of the labeling.

8.5 Educational Benefits of Self-Management with Oxytrol

As previously discussed, self-management characterized by lifestyle modifications and symptom concealment is the norm for this condition. Switching Oxytrol to OTC status would be an advance by allowing access to an effective self-care option that can improve the quality of life and reduce the level of under-treatment. In addition there will be secondary benefits that:

- will help to de-stigmatize this condition.
- include educational efforts which will help to encourage dialogue between women and their health care providers about urinary health in general.
- will introduce new sources of information about other diseases like UTI, DM, and BC that can cause some urinary symptoms like UTI, DM and BC.

The education efforts in the label combined with a collaborative educational campaign will help to inform women not only about how to manage OAB but educate them on other conditions that may share similar symptomatology to OAB. Merck commits to work in conjunction with several prominent professional and consumer organizations including:

- American Urogynecologic Society
- Nurse Practitioner's in Women's Health
- National Association for Continence
- Simon Foundation for Continence
- Alliance for Aging Research
- Society for Women's Health Research

These initiatives aim to educate women that OAB is a treatable medical condition and not a normal part of aging with which they simply must cope. Women will learn about pharmacologic options and behavioral strategies available e to improve their overall outcomes. Programs will be directed to consumers and health care professionals alike, with the ultimate goal of increasing open, honest communication about urinary health.

These educational programs will be multi-faceted including in-office and online brochures and quizzes to help make conversations between women and their health care providers easier, educational articles featured both in print and online, and a rich public relations campaign including spokespersons women can relate to. These efforts are designed to reach a broad range of demographic and socioeconomic audiences. Success will be evaluated via attitude, awareness, and usage surveys to measure how much the educational content has shifted current behaviors related to managing OAB.

8.6 Potential Risks Associated with OTC Access to OAB Therapy

As the label has been shown through extensive study to successfully guide correct self-selection and de-selection among the majority of women choosing to self-manage this condition, the risk assessment related to the availability of Oxytrol in an OTC setting is reduced to a very small cohort of users who might use the product incorrectly. In this case, the inherent safety of the product and the natural history of any non-OAB conditions they might have, should not lead to any unacceptable risks or consequences. The theoretical risks from making Oxytrol available OTC are the potential delays in diagnosis and subsequent treatment of UTI, diabetes, bladder cancer, and pregnancy. However, it seems reasonable that those same risks already exist in the current situation where women manage OAB on their own without an effective treatment option or informative product labeling. Furthermore, the clinical characteristics of these possible underlying conditions allow for an appropriate short trial of nonprescription Oxytrol without presenting additional risk compared to women continuing to self-manage and cope with OAB or the undiagnosed underlying condition.

UTI: As previously discussed, UTIs typically present acutely with dysuria, and/or hematuria, cloudy/foul-smelling urine, and abdominal or flank pain as the condition progresses. There is a sudden onset of frequency/urgency with a UTI, while frequency/urgency associated with OAB is gradual in nature, developing over months and years. The Oxytrol label emphasizes that these symptoms must be present for more than 3 months and women should consult a physician if these other non-OAB symptoms are present to reduce the risk of confusing recent onset frequency and urgency with OAB. Further, with the possible exception of urinary frequency, Oxytrol will not effectively relieve UTI symptoms and the label warns to stop using Oxytrol and see a physician if there is no improvement in 2 weeks.

Diabetes: The American Diabetes Association reports that about 26 million people in the United States have some form of diabetes, and about 7 million of these people are estimated to be currently undiagnosed (2011 National Diabetes Fact Sheet). Type 2 diabetes, which is most relevant for the OAB target population, often goes undiagnosed because it has no symptoms or the symptoms seem benign. Most new cases of diabetes are found during routine health exams and/or blood work, not because a patient seeks help for a specific symptom. While urgency and nocturia can be presenting symptoms for DM, few initial diagnoses are based upon these symptoms alone. The proposed OTC label will instruct patients with a family history of DM, or those with symptoms suggestive of DM as a cause of urinary frequency, to consult with a physician prior to using the product. In addition, the 2-week period of therapy will not effectively treat urinary symptoms that are due to diabetes, including polyuria and polydipsia, the hallmarks of the disease. Thus, it is highly unlikely that symptoms of OAB will mask diagnosis of diabetes. Even if there were a delay in obtaining an appropriate diagnosis of DM due to short-term treatment with Oxytrol, such delay would be unlikely to impact the course of DM treatment. This, combined with the fact that most women are currently managing urinary symptoms with absorbent products, demonstrates that the presence of Oxytrol in an OTC setting would pose minimal, if any, incremental risk in delaying diagnosis of diabetes.

Bladder Cancer: The National Cancer Institute reports that 0.32% of women between the ages of 50-70 have the probability of developing bladder cancer (National Cancer Institute SEER Website). Although rare in women, BC can start with symptoms of frequency and urgency. However, in contrast to OAB, the primary symptom associated with bladder cancer, especially early in the progression of disease, is gross hematuria. Hematuria, gross or microscopic, chronic or intermittent, is the presenting symptoms in 85-90% of patients with bladder cancer. The OTC labeling warns consumers to not use if blood is present in the urine. In addition, consumers are unlikely to obtain relief from their BC symptoms with Oxytrol. Again, the label guides consumers to stop use and talk to a doctor if there is no improvement in two weeks, if their condition worsens, or if new symptoms appear.

Pregnancy: Pregnancy is another condition which could cause urinary frequency/urgency. However, other than the obvious symptom of a missed menstrual period, early pregnancy signs can also include spotting or a very light menstrual period, tender breasts, being tired, having an upset stomach or nausea, feeling bloated, and mood changes (Rogers 2011). Since the proposed OTC label states that OAB symptoms should be present for 3 months, the rate of undiagnosed pregnancy with only the symptoms of frequency or urgency would be extremely low. In addition, OAB is much more prevalent in older, post-menopausal women, also reducing potential risk. Furthermore, the cause of increased urinary frequency in pregnant women is not related to altered function of the bladder detrusor muscle, and it is unlikely that a short course of Oxytrol will improve symptoms. A more likely scenario is that a pregnant woman who inappropriately tries Oxytrol for such symptoms will quickly stop use. In addition, the Pregnancy Category B status for oxybutynin recognizes that there are no demonstrated mutagenic, teratogenic, or toxic effects on the fetus in animal models and no reported evidence in humans.

8.7 Effective Labeling Reduces Potential Risks to Acceptable Levels

With the results of the label comprehension and self-selection studies taken in totality, it can be predicted that the Oxytrol Drug Facts label is about 80% to 95% effective in communicating key messages regarding self-recognition of OAB and product use. Once a woman decides to use the product, the CONTROL study tells us that the label is 80% to 95% effective in driving appropriate ongoing use decisions about when to stop or continue use. Using the self-management labeling safeguards explained in Section 8.3 and a conservative point estimate of 80% correct at each step of self-selection and actual use, where 20% are assumed to make an incorrect decision, it could be calculated (0.2 x 0.2 = 0.4) that about 4% of users might be at some level of medical risk after an initial course of therapy with OTC Oxytrol.

This, of course, is a theoretical extrapolation of the study results, but allows one to better understand the dimension of the potential level of risk. This risk is further mitigated by the fact that a potential delay of a few weeks in the diagnosis of the other related conditions of concern does not create an unacceptable risk. **Furthermore, and perhaps most importantly, these risks already exist in the population currently managing OAB on their own, whether or not Oxytrol has been introduced as an OTC treatment option.**

8.8 Conclusions

- Nonprescription Oxytrol will increase access to a proven treatment option associated with improved daily life for women currently using self-management strategies to deal with their OAB.
- A comprehensive education program will inform women about other potential causes of urinary frequency and urgency and outline both behavioral strategies and pharmacological treatments which can help them more effectively manage their urinary health.
- These overall benefits outweigh the potential risk of delay in diagnosis of an underlying disease that produces OAB-like symptoms.
- These factors should lead to a decrease in untreated OAB, earlier diagnosis of other related conditions that can cause OAB-like symptoms, and an overall, albeit unproven, improvement in public health as women gain more understanding of OAB and bladder health in general.

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Responder Analyses of Phase 3 Trials

A post-hoc responder analysis was performed using both of the two phase 3 trials (study O99009 and O00011). Responders were defined by using clinically meaningful measures for the primary endpoint and 2 key secondary endpoints at the end of the study (week 12). The following efficacy measures were used to define responders at the end of 12 weeks of treatment:

- Urinary incontinence: 100% and 50% decrease in incontinence episodes
- Urinary frequency: 10% , 20% or 30% reduction in urinary frequency
- Urinary volume: 10% , 20% or 30% increase in urinary volume

Subgroup analyses were performed for gender and age. For the male subjects' population, the sample size of the responders was ascertained to be very small for any statistical interpretation. Age groups were grouped as either less than 65 years or at and above 65 years of age. All above mentioned responder analysis was performed separately for each gender and age groups.

Pooled analysis was based on data from these two phase 3 studies. Pooled data increase the sample size resulting in an increase of the power of the efficacy analysis. The rational of the pooled analysis is based on the following characteristics:

- Similar Study Design: both trials were double-blind, placebo control studies; both studies had the same dosage of 3.9 mg oxybutynin per day and same duration of double-blind treatment of 12 weeks.
- Similar Endpoints: both of the pooled studies had similar primary and secondary endpoints of:
  - Primary endpoint: change of number of urinary incontinence episodes
  - Key secondary endpoints:
    - Change of urinary frequency and
    - urinary volume per void
- Consistent individual study effect, similar drop-off rate.
- Similar study population: both of the studies enrolled intent to treat population suffering from same disease (Over Active Bladder or OAB). These patient populations had very similar and comparable baseline characteristics specifically of age, gender, severity (baseline number of urinary incontinence episodes, baseline urinary frequency, and baseline urinary volume).
- The intent to treat patients enrolled in O99009 were either naive or pre-treated with other OAB medications; study O00011 only enrolled intent to treat patients who were pre-treated with other OAB medications.

- Both of the trials (O99009 and O00011) had suitable washout period prior to disposing study or placebo medications. In any of the pooled analyses, it was stratified by study to control the within study variance.

Descriptive analysis was conducted for individual study data and for the pooled data. Baseline mean and standard deviation were summarized by treatment group for individual study as well for the pooled data. Number of responders and responding rate for each individual study and pooled studies was provided by treatment group. For each individual study, Fisher exact test was conducted to compare the difference of responder rate by treatment group. For pooled data, CMH (Cochran-Mantel-Haenszel) Test was conducted to compare the difference of responder rates between oxybutynin TDS (study arm) and placebo while controlling for study. Heterogeneity between studies was evaluated by using Breslow-Day test. Treatment group comparisons of binary responder data was also explored by using logistic regression model adjusted by baseline value, study and pooled center.

For all patients, at 12 weeks of treatment the study group (oxybutynin TDS) subjects in comparison to placebo group showed statistically significant reduction in the urinary incontinence episodes and in urinary frequency. A similar statistically significant increase in urinary volume was also noted in the study group responders when compared with the placebo group responders. Detailed data is shown in Table 1 below.

Table 1 Results of responder analysis for all patients (Pooled data from Phase 3 studies O99009 and O00011)

All patients		Placebo			oxybutynin TDS			
		N	R	% R	N	R	% R	P*
Urinary Frequency	A. 10 % reduction	243	130	53.5%	239	152	63.6%	0.0235
Urinary Frequency	B. 20 % reduction	243	84	34.6%	239	114	47.7%	0.0035
Urinary Frequency	C. 30 % reduction	243	46	18.9%	239	61	25.5%	0.0821
Urinary Volume per Void	A. 10 % increase	243	100	41.2%	239	133	55.6%	0.0016
Urinary Volume per Void	B. 20 % increase	243	66	27.2%	239	105	43.9%	0.0001
Urinary Volume per Void	C. 30 % reduction	243	44	18.1%	239	86	36.0%	<0.0001

Notes: R = Responders, %R = %Responders, *Comparison significant if p ≤ 0.05

For all female subjects at 12 weeks of treatment the study group (oxybutynin TDS) subjects in comparison to placebo group showed statistically significant reduction in the urinary incontinence episodes and in urinary frequency. A similar statistically significant increase in urinary volume was also noted in the study group responders when compared with the placebo group responders. Detailed data is shown in Table 2 below.

Table 2 Results of responder analysis for all female subjects (Pooled data from Phase 3 studies O99009 and O00011)

All female pts.		Placebo			oxybutynin TDS			
		N	R	% R	N	R	% R	P
Urinary Frequency	A. 10 % reduction	225	120	53.3%	218	137	62.8%	0.0405
Urinary Frequency	B. 20 % reduction	225	78	34.7%	218	103	47.2%	0.0072
Urinary Frequency	C. 30 % reduction	225	43	19.1%	218	53	24.3%	0.1841
Urinary Volume per Void	A. 10 % increase	225	94	41.8%	218	125	57.3%	0.0011
Urinary Volume per Void	B. 20 % increase	225	65	28.9%	218	99	45.4%	0.0003
Urinary Volume per Void	C. 30 % reduction	225	44	19.6%	218	82	37.6%	<0.0001

Notes: R = Responders, %R = %Responders, *Comparison significant if $p \leq 0.05$

The goal of this post-hoc responder analysis was to determine whether a treatment effect was clinically meaningful in the study population at twelve weeks of treatment. As a limitation, rejection of either null hypothesis via responder analysis simply allows one to conclude that there is a non-zero difference between the groups, not that the difference is clinically meaningful. Another well-known limitation of the responder analysis is reduced power in comparison to the original scale analysis submitted by the Sponsor with the NDA 21-351 in the year 2003.

Overall for all the patient population as well as for the all-female subject population, the treatment effect in the oxybutynin TDS study group in comparison to placebo was statistically different and clinically meaningful for the improvement in urinary incontinence (100% and 50% decrease in incontinence episodes), urinary frequency (10% and 20% reduction) and urinary volume per void (10%, 20% and 30% increase in urinary volume) following 12 weeks of treatment.

REVIEW OF QUALITY OF LIFE DATA FROM PHASE 3 AND PHASE 4

Clinical efficacy data collected to date demonstrate that oxybutynin TDS significantly improves urinary incontinence episodes, urinary frequency, and urinary void volume. Instruments that measure patient's quality of life (QoL) provide additional information of how the clinical improvements are meaningful to the patient. This appendix summarizes QoL data collected to date, from two Phase 3 studies and one Phase 4 study.

QoL data from Phase 3 Studies

Both Phase 3 trials (study O99009 and O00011) evaluated quality of life (QoL) using the Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory (UDI). These studies including the QoL data results were reviewed as part of the original NDA 21-351 which was approved in 2003. Brief summary reviews of the QoL data are presented here.

IIQ was developed to assess the psychosocial impact of urinary incontinence in women and consists of 30 items (24 on the degree to which incontinence affects activities and 6 on the feeling engendered. Scores are obtained overall or for four subscales determined by factor and cluster analysis: physical activity, travel, social relationships and emotional health. The IIQ has been found to have acceptable levels of reliability and validity across a range of studies (*3rd International Consultation on Incontinence, 2005*). In the IIQ survey (Table 1), enrolled subjects with OAB rated impact on 24 activities including: ability to do household chores, ability to travel by car for more than 20 minutes, employment outside the home, participation in social activities outside the home, hobbies and pastime activities, physical recreation, and having friends visit your home. Scoring for the IIQ was conducted as follows: Responses on the degree to which urinary incontinence affects each activity or feeling ranged from 0 = “not at all” to 3 = “greatly.” Mean scores were calculated for each subscale. These scores were then transformed by subtracting one and multiplying by 100/3 to convert to a common scale of 0-100. The total score was given by the sum of all subscale scores and ranged from 0 to 400. A decrease in mean score represented improvement. Subjects were asked to rank on a scale of 1 to 4 the degree to which a symptom bothered them (1 = “not at all”, 4 = “greatly”).

The UDI questionnaire (Table 2) was developed in the US with women to assess the degree to which symptoms associated with incontinence are troubling. It contains 19 lower urinary tract symptoms and has shown to have high levels of validity, reliability and responsiveness in a community dwelling population of women with incontinence. Male patients were instructed to skip questions pertained specifically for women. The scoring system for the UDI was similar to that of the IIQ. Similar to the IIQ, a decrease in score represented improvement (*3rd International Consultation on Incontinence, 2005*).

Table 1 Items in the Incontinence Impact Questionnaire (IIQ)

Has urine leakage affected	
Physical activity (6 items)	Household chores Maintenance or repair work Shopping activities Hobbies and part-time activities Physical recreational activities Physical health
Social relationship (10 items)	Church or temple attendance Volunteer activities Having friends visit in home Participating in social activities outside home Relationship with friends Relationship with family excluding husband/ companion Sexual relations Way you dress Fear of odor restrict activities Fear of embarrassment restrict activities
Travel (6 items)	Entertainment activities Travel for distance less than 20 min from home Travel for distance more than 20 min from home Going to place if not sure about restrooms Going on vacation Employment outside the home
Emotional health (8 items)	Emotional health Sleep Nervousness or anxiety Fear Frustration Anger Depression Embarrassment

Table 2 Items in the Urogenital Distress Inventory (UDI)

Do you experience, and, if so, how much are you bothered by:	
Irritative symptoms (6 items)	Frequent urination Feeling of urgency Urine leakage related to the feeling of urgency Large amounts of urine leakage Nighttime urination Bedwetting
Obstructive/discomfort (11 items)	Urine leakage not related to urgency or activity Difficulty emptying bladder Feeling of incomplete bladder emptying Lower abdominal pressure Pain when urinating Pain in the lower abdominal or genital area Heaviness or dullness in the pelvic area Feeling of bulging or protrusion in the vaginal area Bulging or protrusion that can see in the vaginal area Pelvic discomfort when standing or physically exerting Have to push on the vaginal walls to have a bowel movement
Stress symptoms (2 items)	Urine leakage related to physical activity, coughing or sneezing Small amounts of urine leakage

In study O99009, during the double-blind period, the IIQ total scores showed a significant positive effect of 39 cm^2 oxybutynin TDS treatment at the end of treatment (EOT) in comparison with placebo. This effect was also demonstrated for several IIQ subscales at various post-baseline time points. In the 39 cm^2 treatment group, mean IIQ total score decreased approximately 39% at EOT in comparison with an improvement of about 28% for placebo ($p = 0.0327$). Similar improvements were also seen in the following subscales: physical activity (ability to do household chores) ($p = 0.0472$); ability to travel ($p = 0.0115$); and emotional health ($p = 0.0480$). Overall, average UDI scores generally decreased from baseline showing lesser degree of trouble with the symptoms associated with incontinence. The decrease in total UDI score for females was statistically significant at EOT in comparison with placebo ($p = 0.0266$) for the oxybutynin TDS 39 cm^2group.

In Study O00011, patient QoL was improved during oxybutynin TDS treatment, indicated by total IIQ score ($p = 0.0271$) and trends in UDI. Individual IIQ subscales (travel, social relationships, emotional health, and physical activity) improved in general, but the magnitude of change was significant only for the improved ability for travel ($p = 0.0018$). For oxybutynin TDS, the magnitude of this change was not significant when compared to placebo at EOT except for irritative symptoms ($p = 0.0156$).

QoL data from Phase 4 Study (MATRIX)

The long-term effects of Oxybutynin Transdermal System (Oxytrol) on OAB patients' quality of life (QoL) was evaluated in MATRIX, a multi-center community-based naturalistic open-label, Phase 4 study. Adult subjects with one or more symptoms of overactive bladder (urge urinary incontinence, urgency, and/or frequency) were treated with oxybutynin TDS (3.9 mg/day every 4 days) for up to 6 months. Patients underwent QoL assessments at baseline, at Month 3, and at Month 6 by answering 3 validated questionnaires:

- The King's Health Questionnaire (KHQ) for the assessment of health-related QoL
- The Beck Depression Inventory (BDI) for the evaluation of the existence and severity of symptoms associated with depression, and
- The Work Productivity Questionnaire (WPQ) for the estimation of work activity impairment and productivity loss

The study was conducted after oxybutynin TDS was approved for use in 2003. More than 2500 patients (N=2878) were enrolled to ensure that each of the 3 above-mentioned QoL assessments would have at least 467 completers to detect a 3% changes from baseline, with 90% of power (1-β) and a significance level (α) of 0.05.

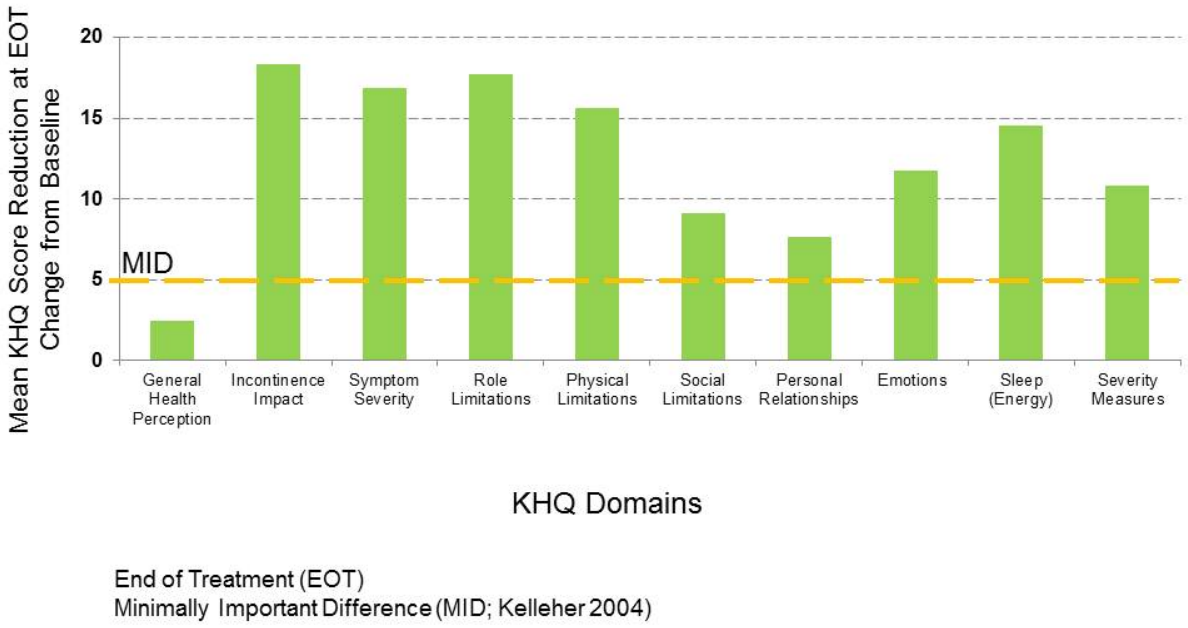
Health-related QoL

Health-related QoL was assessed using King's Health Questionnaire (KHQ). The International Consultation on Incontinence (ICI) ranks this instrument as a Grade A (Highly Recommended) QoL questionnaire for OAB symptoms and for impact of urinary incontinence (3rd ICI 2005). King's Health Questionnaire consists of 2 single-item domains (General Health Perceptions and Incontinence Impact), 7 multi-item domains (Role Limitations, Physical Limitations, Social Limitations, Personal Relationships, Emotions, Sleep/Energy, Severity/Coping), and a multi-item Symptom Severity scale (Kelleher 1997). The 2 single-item domains and the 7 multi-item domains of the KHQ are scored on a scale from 0 (best) to 100 (worst). The Symptom Severity scale is scored from 0 (best) to 30 (worst). Decreases in KHQ domain scores indicate an improvement in health-related QoL. Figure 1 shows patients' categorical KHQ scores (Mean ± SD) at baseline, Month 3, and Month 6. Notably, patients' health-related QoL were severely affected by OAB or incontinence conditions.

In each of the 10 KHQ domains, patients' KHQ scores were notably high at baseline, indicating severely affected QoL prior to the treatment. Following the oxybutynin TDS treatment, significant score reductions were observed at Month 3 ($p<0.0001$ for all 10 domains) and Month 6 ($p<0.0001$ for all 10 domains). Except for the General Health Perceptions, where the mean score change from baseline at EOT was -2.4, all the other 9 KHQ domains had a mean score reduction of larger than 5 points (Figure 1), a criteria known as the Minimally Important Difference (MID), the clinically meaningful or the smallest change in score that subjects perceive as beneficial (Kelleher 2004). In Symptom Severity domain, for example, where patients were asked whether their urinary frequency, nocturia, urgency, urge, intercourse incontinence, or nocturnal enuresis condition had improved, worsened, or stayed the same, significant numbers of patients reported that their conditions had improved after the oxybutynin TDS treatment; the summary score of the domain was therefore significantly reduced at EOT, with the mean score reduction of -16.8 ($p<0.0001$), which was not only statistically significant but also clinically meaningful. Similar results were observed across the remaining KHQ domains, each indicates a clinically significant improvement of QoL in OAB patients treated with oxybutynin TDS.

Figure 1 Mean KHQ Score Reduction in OAB Patients Following a 6-Month Oxybutynin TDS Treatment

(Source: MATRIX Study Data)



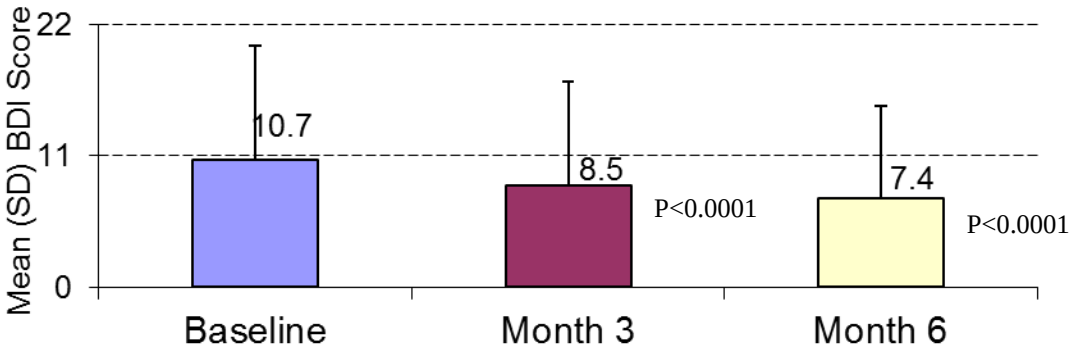
End of Treatment (EOT)
Minimally Important Difference (MID; Kelleher 2004)

Mental Health QoL

Patients were also evaluated for the existence and severity of symptoms associated with depression, using Beck Depression Inventory (BDI) (Beck, 1961, 1996). The BDI is one of the most commonly used self-reported tools for the measurement of depression. It assesses the severity of both cognitive and somatic aspects of depression (Aalto 2012). The BDI has short and long versions: BDI-6, BDI-13, and BDI-21. The study used the 21-item version, which has demonstrated sound psychometric properties across populations (Beck 1984, Knight 1984, Gatewood-Colwell 1989, Ambrosini 1991, Shafer 2006, Nuevo 2009). The 21-item BDI is scored from 0 (best) to 63 (worst). Decreases in BDI scores indicate an improvement from depression. In Study MATRIX, the BDI summary scores in patients treated with oxybutynin TDS were 10.7±9.51 (N=2581, Median 8.0) at baseline, 8.5±8.7 (N=1668, Median 6.0) at Month 3, and 7.4±7.76 (N=1379, Median 5.3) at Month 6, respectively (Figure 2). Notably, the mean BDI score at baseline was very close to the borderline defined for mild mood disturbance (BDI 11-16) and some patients had exceeded the score of 17 where a medical treatment might be needed (Beck 1996). The BDI score reductions at Month 3 and Month 6 were -2.0±6.62 and -2.8±7.08, respectively; both were statistically significant ($p < 0.0001$).

Figure 2 Mean (SD) BDI Score of OAB Patients at Baseline and at Month 3 and Month 6 of Oxybutynin TDS Treatment

(Source: MATRIX Study data)

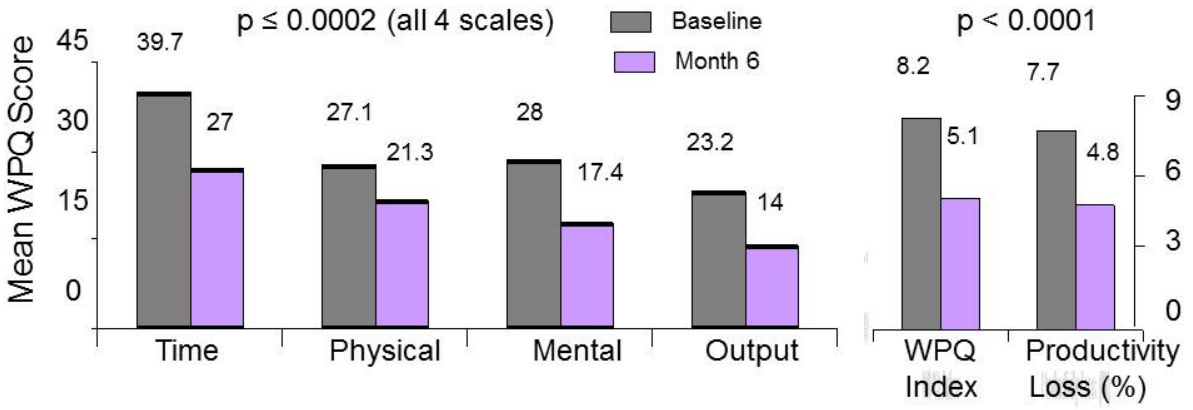


Work activity impairment and productivity loss

The work activity impairment and productivity loss were assessed using the Work Productivity Questionnaire (WPQ), an abbreviated, 8-question version of the Work Limitations Questionnaire (WLQ). The WLQ has been validated with chronic condition groups such as depression, osteoarthritis, back pain, migraine and epilepsy (Lerner 1998, 2001, 2002) and has been employed in a wide range of studies across different occupational and patient groups reporting a range of chronic conditions (Burton 2004, Munir 2007, Feuerstein 2007, Schmitt 2006). Responses to the 8 items were combined into 4 work limitation scales: Time Management, Physical Demands, Mental/Interpersonal, and Output Demands. Scale scores ranged from 0 (best) to 100 (worst). In addition to the scale score, a total WPQ index score was calculated and converted into an estimate of productivity loss. Changes from baseline were analyzed using two-tailed, paired t-test. Significant WPQ score reductions were observed in all 4 work limitation scales ($p \leq 0.002$), the total WPQ Index ($p < 0.0001$) and Productivity Loss ($p < 0.0001$; Figure 3), at both Month 3 and Month 6 (Figure 3).

Figure 3 Mean WPQ Score in OAB Patients at Baseline and at Month 6 of oxybutynin TDS Treatment

(Source: MATRIX Study data)



The mean Productivity Loss at baseline, Month 3, and EOS in Month 6 were 7.7%, 5.5%, and 4.8%, respectively, with the median changes from baseline of -2.2 and -2.9%. For a full-time employee who works 40 hours per week, a reduction in Productivity Loss of 2.9% is equivalent to a gain of ~60 hours/year, about 1 ½ working week per year.

OAB has a profound impact on patient's overall quality of life. At baseline, 43% of patients reported that they could not enjoy things as much as they used to; 46% had worse concentration difficulty; 52% became less interested in sex or completely lost interest; 68% got tired or fatigued more easily and 71% of patients reported having less energy. All were attributed to the associated bladder problem. At the end of the oxybutynin TDS treatment, the percent of patients having the above-listed issues dropped to 33%, 34%, 39%, 53%, and 63%, respectively (all $p < 0.0001$). This indicates that after the oxybutynin TDS treatment, ~30-35% of patients were able to regain their ability to enjoy things they used to.

SAEs reported in Clinical Development

Treatment	Patient ID	Age (*yr*), Gender (M/F)	Description of Event, Hospitalized (yes/no)	Duration	Treatment Related (*yes/no*)	Resolution
Study O96017						
15 mg/day oral Oxybutynin	50055	73, F	Bronchitis, *yes*	3 days	No	resolved; completed study
39 cm^2 Oxybutynin TDS	50024	67, F	Renal Calculus, *yes*	48 days	No	resolved; completed study
Study 099009 – Double Blind						
Placebo	60321	56, F	Aggravated hypertension, *yes* Thrombosis coronary, yes Aneurysm, yes	6 days - 6 days	No No No	resolved, continuing, resolved, completed study
	60412	72, F	Inflicted injury, *yes*	5 days	No	resolved, completed study
	60524	82, F	Arthropathy, *yes*	3 days	No	resolved, completed study
	61010	50, F	MS aggravated, *yes*	5 days	No	resolved, completed study
	62116	63, M	Chest pain, *yes*	8 days	No	resolved, discontinued
	63419	61, F	Arthralgia, *yes*	3 days	No	resolved, completed study
13 cm^2 Oxybutynin TDS	60904	67, F	Diarrhea, *yes*	5 days	No	resolved, continued[1]
	61709	66, F	Pneumonia, *yes* Dyspnea, yes Sepsis, yes	25 days 25 days 25 days	No No No	resolved, discontinued
	62130	82,F	Surgical intervention, *yes*	5 days	No	resolved, completed study

Treatment	Patient ID	Age (*yr*), Gender (M/F)	Description of Event, Hospitalized (yes/no)	Duration	Treatment Related (*yes/no*)	Resolution
			Chronic obstructive airway disease, yes	15 days	No	resolved, completed study
	63311	82, F	Syncope, *yes*	7 days	No	resolved, discontinued
26 cm^2 Oxybutynin TDS	61305	59, F	Chest pain, *yes*	2 days	No	resolved, discontinued
	61730	81, F	Surgical intervention, *yes*	6 days	No	resolved, continued[2]
	62702	76,F	Angina pectoris, *yes*	2 days	No	resolved, completed study
39 cm^2 Oxybutynin TDS	61623	83, F	Angina pectoris, *yes*	2 days	No	resolved, completed study
	63609	40,F	Pancreatitis, *yes*	38 days	No	resolved, discontinued
Study 099009 – Open Label						
13 cm^2 Oxybutynin TDS	61801	73, F	Gout, *yes*	7 days	No	resolved, continued[3]
	62107	74, F	Arthritis, *yes*	6 days	No	resolved, completed study
	62118	67, F	Chest pain, *yes*	24 days	No	resolved, discontinued
26 cm^2 Oxybutynin TDS	61519	50, F	Inflicted injury, *yes*	9 days	No	resolved, continued[4]
	61801	73,F	Endometrial neoplasm malignant, *no*	4 days	No	resolved, discontinued
	61803	83, M	Atrial fibrillation, *yes*	4 days	No	resolved, completed study
	61813	66, F	Chest pain, *yes*	6 days	No	resolved, completed study
39 cm^2 Oxybutynin TDS	64028	80, F	Transient ischemic attack, *yes* Gastroesophageal reflux, *yes*	5 days 2 days	No No	resolved, completed study

APPENDIX 3 SAES REPORTED IN CLINICAL DEVELOPMENT

Treatment	Patient ID	Age (*yr*), Gender (M/F)	Description of Event, Hospitalized (yes/no)	Duration	Treatment Related (*yes/no*)	Resolution
Study O99009 - Extension						
13 cm^2 Oxybutynin TDS	62121	71, M	Arthropathy, *yes* Surgical intervention, yes	16 days 17 days	No No	resolved, completed study
26 cm^2 Oxybutynin TDS	60318	41, F	Bradycardia, *yes*	3 days	No	resolved, completed study
	64005	67, F	Back pain, *yes*	11 days	No	resolved, completed study
	64041	81, F	Aortic stenosis, *yes*	20 days	No	resolved, completed study
39 cm^2 Oxybutynin TDS	60330	71, F	Cerebrovascular disorder, *yes*	6 days	No	resolved, completed study
	61125	74, M	Hydrocephalus, *yes*	-	No	continuing, completed study
	64024	65, F	Gastroenteritis, *yes*	7 days	No	resolved, completed study
Study O00011 – Double Blind						
Placebo	90110	65, F	Surgical intervention, *yes*	12 days	No	resolved, completed study
	93701	71, F	Transient ischemic attack, *yes*	3 days	No	resolved, completed study
	94509	66, M	Hernia NOS, *yes*	5 days	No	resolved, completed study
39 cm^2 Oxybutynin TDS	92701	87, M	Cerebrovascular disorder, *yes*	5 days	No	resolved, completed study
	94407	76, F	Bradycardia, *yes* Syncope, yes Hypotension	7 days 7 days 7 days	No No No	resolved, discontinued resolved, discontinued resolved,

Treatment	Patient ID	Age (*yr*), Gender (M/F)	Description of Event, Hospitalized (yes/no)	Duration	Treatment Related (*yes/no*)	Resolution
			postural, yes			continued[5]
	94518	46, F	Back pain, *yes*	33 days	No	resolved, discontinued

[1] Patient 60904 discontinued after experiencing application site erythema.

[2] Patient 61730 discontinued after experiencing dizziness.

[3] Patient 61801 discontinued after experiencing endometrial neoplasm malignant while being dosed at 25 cm2 Oxybutynin TDS.

[4] Patient 61519 was discontinued from study due to noncompliance.

[5] Patient 94407 was discontinued after experiencing bradycardia and syncope.

Data from Table 8.8-1. NDA 21-351, Section 8, Integrated Summary of Safety, Watson, Pharmaceuticals, 2002.

Adverse events by System Organ Class from MATRIX study (>1% of all reported AEs)

SOC	BIEPE Treatment Group (N=1598)			OC Treatment Group (N=1283)			Study Safety Population (N=2881)		
	Subjects	% N	AEs	Cases	% N	AEs	Subjects	% N	AEs
General disorders & administration site conditions	297	19%	415	207	16%	317	504	18%	732
Skin & subcutaneous tissue disorders	176	11%	231	140-	11%	166	316	11%	397
Gastrointestinal disorders	154	10%	192	116	9%	161	270	9%	353
Infections & infestations	144	9%	188	103	8%	147	247	9%	335
Nervous system disorders	92	6%	111	77	6%	101	169	6%	212
Musculoskeletal & connective tissue disorders	67	4%	82	40	3%	58	107	4%	140
Renal & urinary disorders	50	3%	63	37	3%	45	87	3%	108
Respiratory, thoracic & mediastinal disorders	45	3%	60	33	3%	47	78	3%	107
Injury, poisoning & procedural complications	30	2%	32	32	3%	51	62	2%	83
Psychiatric disorders	37	2%	42	22	2%	27	59	2%	69
Eye disorders	25	2%	29	23	2%	27	48	2%	56
Surgical & medical procedures	26	2%	30	13	1%	13	39	1%	43
Reproductive system & breast disorders	18	1%	20	10	1%	14	28	1%	34
Metabolism & nutrition disorders	14	1%	14	14	1%	19	28	1%	33

(Source: Data from Table 14.21, MATRIX CSR)

Table 1 CONTROL: Clinical Summary and Disposition of Oxytrol Users with Adverse Experiences

	No. of Users	% of 785 Users	% of 519 Subjects with AEs
With one or more adverse experience(s)	519	66.1%	-
With serious adverse experience(s)	35	4.5%	-
Deaths from serious drug-related adverse experience(s)	0	0.0%	0.0%
Stopped using Oxytrol then restarted (all reasons for stopping)	42	5.4%	8.1%
Stopped using Oxytrol permanently (all reasons for stopping)	152	19.4%	29.3%
Stopped using Oxytrol then restarted due to adverse experiences [a]	21	2.7%	4.0%
Stopped using Oxytrol permanently due to adverse experiences [a]	110	14.0%	21.2%
Stopped using Oxytrol due to serious adverse experiences	13	1.7%	2.5%
Serious drug-related adverse experiences lost to follow-up [a,b]	1	0.1%	0.2%

[a] Relationship to drug therapy determined as 'possible' or 'probable'.

[b] This subject was lost for follow-up. The verbatim field "other" (CRF variable AEOTH) recorded "Last patch was applied on 23-Sep because she thought she was going to have an outpatient. procedure. Has had no patches available to apply since then."

Source: CONTROL CSR Table 75

Table 2: CONTROL: Adverse Events by Severity

AE Severity	Mild				Moderate				Severe				Total			
MedDRA System Organ Class	AE	%AE (975)	N (Subjects, 785)	%N (785)	AE	%AE (975)	N (Subjects, 785)	%N (785)	AE	%AE (975)	N (Subjects, 785)	%N (785)	AE	%AE (975)	N (Subjects, 785)	%N (785)
Cardiac disorders	1	0.1%	1	0.1%	1	0.1%	1	0.1%	2	0.2%	2	0.3%	4	0.4%	4	0.5%
Ear and labyrinth disorders	3	0.3%	3	0.4%	1	0.1%	1	0.1%	0	0.0%	0	0.0%	4	0.4%	4	0.5%
Eye disorders	21	2.2%	20	2.5%	11	1.1%	11	1.4%	0	0.0%	0	0.0%	32	3.3%	31	3.9%
Gastrointestinal disorders	103	10.6%	87	11.1%	15	1.5%	15	1.9%	1	0.1%	1	0.1%	119	12.2%	103	13.1%
General disorders and administration site conditions	193	19.8%	180	22.9%	11	1.1%	11	1.4%	1	0.1%	1	0.1%	205	21.0%	192	24.5%
Hepatobiliary disorders	0	0.0%	0	0.0%	0	0.0%	0	0.0%	3	0.3%	3	0.4%	3	0.3%	3	0.4%
Immune system disorders	10	1.0%	10	1.3%	1	0.1%	1	0.1%	1	0.1%	1	0.1%	12	1.2%	12	1.5%
Infections and infestations	151	15.5%	129	16.4%	55	5.6%	44	5.6%	6	0.6%	6	0.8%	212	21.7%	179	22.8%
Injury, poisoning and procedural complications	9	0.9%	9	1.1%	20	2.1%	17	2.2%	8	0.8%	7	0.9%	37	3.8%	33	4.2%
Investigations	10	1.0%	10	1.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	10	1.0%	10	1.3%
Metabolism and nutrition disorders	11	1.1%	11	1.4%	3	0.3%	3	0.4%	1	0.1%	1	0.1%	15	1.5%	15	1.9%
Musculoskeletal and connective tissue disorders	36	3.7%	31	3.9%	32	3.3%	28	3.6%	3	0.3%	3	0.4%	71	7.3%	62	7.9%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0.5%	5	0.6%	1	0.1%	1	0.1%	1	0.1%	1	0.1%	7	0.7%	7	0.9%
Nervous system disorders	51	5.2%	45	5.7%	17	1.7%	17	2.2%	4	0.4%	4	0.5%	72	7.4%	66	8.4%
Psychiatric disorders	7	0.7%	7	0.9%	8	0.8%	7	0.9%	2	0.2%	2	0.3%	17	1.7%	16	2.0%
Renal and urinary disorders	55	5.6%	50	6.4%	15	1.5%	13	1.7%	0	0.0%	0	0.0%	70	7.2%	63	8.0%

APPENDIX 5 CONTROL ADVERSE EXPERIENCES

AE Severity	Mild				Moderate				Severe				Total			
MedDRA System Organ Class	**AE**	**%AE (975)**	**N (Subjects, 785)**	**%N (785)**	**AE**	**%AE (975)**	**N (Subjects, 785)**	**%N (785)**	**AE**	**%AE (975)**	**N (Subjects, 785)**	**%N (785)**	**AE**	**%AE (975)**	**N (Subjects, 785)**	**%N (785)**
Reproductive system and breast disorders	12	1.2%	12	1.5%	4	0.4%	4	0.5%	1	0.1%	1	0.1%	17	1.7%	17	2.2%
Respiratory, thoracic and mediastinal disorders	28	2.9%	25	3.2%	2	0.2%	2	0.3%	1	0.1%	1	0.1%	31	3.2%	28	3.6%
Skin and subcutaneous tissue disorders	17	1.7%	16	2.0%	5	0.5%	5	0.6%	1	0.1%	1	0.1%	23	2.4%	22	2.8%
Surgical and medical procedures	2	0.2%	2	0.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.2%	2	0.3%
Vascular disorders	7	0.7%	7	0.9%	4	0.4%	4	0.5%	1	0.1%	1	0.1%	12	1.2%	12	1.5%
Total	**732**	**75.1%**	**348**	**44.3%**	**206**	**21.1%**	**139**	**17.7%**	**37**	**3.8%**	**32**	**4.1%**	**975**	**100.0%**	**519**	**66.1%**

% AEs 975 = Total AEs reported in study
% AE 785 = Total AEs reported in each subject. Although a subject may have had two or more adverse experiences, the subjects is counted only once within a category. The same patient may appear in different categories.
Source: CONTROL CSR, Table 14.12.25

Table 3 CONTROL: Adverse Events Reported in Two or More Subjects N=785 (%)

Preferred term	All, N (%)		Mild, N (%)		Moderate, N (%)		Severe, N (%)	
Abdominal discomfort	2	(0.3)	1	(0.1)	1	(0.1)		
Abdominal pain	5	(0.6)	5	(0.6)				
Abdominal pain lower	5	(0.6)	4	(0.5)	1	(0.1)		
Anxiety	4	(0.5)	2	(0.3)	2	(0.3)		
Application site erythema	9	(1.1)	9	(1.1)				
Application site irritation	135	(17.2)	130	(16.6)	5	(0.6)		
Application site pruritus	8	(1.0)	8	(1.0)				
Application site rash	4	(0.5)	4	(0.5)				
Application site reaction	13	(1.7)	12	(1.5)	1	(0.1)		
Arthralgia	10	(1.3)	3	(0.4)	6	(0.8)	1	(0.1)
Arthritis	4	(0.5)	2	(0.3)	2	(0.3)		
Arthropod bite	2	(0.3)	2	(0.3)				
Back pain	18	(2.3)	11	(1.4)	6	(0.8)	1	(0.1)
Balance disorder	2	(0.3)	2	(0.3)				
Blister	2	(0.3)	1	(0.1)			1	(0.1)
Blood cholesterol increased	4	(0.5)	4	(0.5)				
Blood glucose increased	2	(0.3)	2	(0.3)				
Breast tenderness	2	(0.3)	2	(0.3)				
Bronchitis	11	(1.4)	4	(0.5)	7	(0.9)		
Cataract	5	(0.6)	1	(0.1)	4	(0.5)		
Chest pain	3	(0.4)			2	(0.3)	1	(0.1)
Cholecystitis	2	(0.3)					2	(0.3)
Constipation	20	(2.5)	19	(2.4)	1	(0.1)		
Contusion	2	(0.3)	2	(0.3)				
Cough	15	(1.9)	15	(1.9)				
Cystitis	15	(1.9)	9	(1.1)	6	(0.8)		
Decreased appetite	2	(0.3)	2	(0.3)				
Depression	5	(0.6)	2	(0.3)	3	(0.4)		
Diarrhea	16	(2.0)	13	(1.7)	3	(0.4)		
Diabetes mellitus	2	(0.3)			1	(0.1)	1	(0.1)
Diverticulitis	3	(0.4)	2	(0.3)	1	(0.1)		
Dizziness	15	(1.9)	13	(1.7)	2	(0.3)		
Dry eye	10	(1.3)	9	(1.1)	1	(0.1)		
Dry mouth	32	(4.1)	32	(4.1)				
Dry throat	2	(0.3)	2	(0.3)				
Dysgeusia	2	(0.3)	2	(0.3)				
Dysuria	12	(1.5)	9	(1.1)	3	(0.4)		

APPENDIX 5 CONTROL ADVERSE EXPERIENCES

Preferred term	All, N (%)	Mild, N (%)	Moderate, N (%)	Severe, N (%)
Edema peripheral	4 (0.5)	4 (0.5)		
Erythema	2 (0.3)	2 (0.3)		
Excoriation	3 (0.4)	1 (0.1)	2 (0.3)	
Fall	3 (0.4)	1 (0.1)	2 (0.3)	
Fatigue	11 (1.4)	10 (1.3)	1 (0.1)	
Fecal incontinence	2 (0.3)	2 (0.3)		
Flank pain	4 (0.5)	2 (0.3)	2 (0.3)	
Fungal infection	6 (0.8)	6 (0.8)		
Gastroenteritis viral	7 (0.9)	5 (0.6)	2 (0.3)	
Gastroesophageal reflux disease	3 (0.4)	2 (0.3)	1 (0.1)	
Headache	19 (2.4)	15 (1.9)	4 (0.5)	
Hematuria	3 (0.4)	2 (0.3)	1 (0.1)	
Herpes zoster	2 (0.3)	1 (0.1)	1 (0.1)	
Hot flush	2 (0.3)	2 (0.3)		
Hyperhidrosis	2 (0.3)	1 (0.1)	1 (0.1)	
Hyperlipidemia	3 (0.4)	3 (0.4)		
Hypersensitivity	8 (1.0)	6 (0.8)	1 (0.1)	1 (0.1)
Hypertension	8 (1.0)	4 (0.5)	4 (0.5)	
Hypertonic bladder	5 (0.6)	5 (0.6)		
Hypoglycemia	2 (0.3)	1 (0.1)	1 (0.1)	
Infection	2 (0.3)	1 (0.1)	1 (0.1)	
Influenza	18 (2.3)	11 (1.4)	6 (0.8)	1 (0.1)
Insomnia	3 (0.4)	3 (0.4)		
Irritability	3 (0.4)	3 (0.4)		
Joint sprain	3 (0.4)		3 (0.4)	
Joint swelling	3 (0.4)	3 (0.4)		
Melanocytic naevus	2 (0.3)	2 (0.3)		
Menorrhagia	2 (0.3)	2 (0.3)		
Micturition urgency	3 (0.4)	2 (0.3)	1 (0.1)	
Migraine	2 (0.3)		2 (0.3)	
Muscle spasms	5 (0.6)	4 (0.5)	1 (0.1)	
Musculoskeletal pain	3 (0.4)	1 (0.1)	2 (0.3)	
Nasal congestion	2 (0.3)	2 (0.3)		
Nasopharyngitis	45 (5.7)	44 (5.6)	1 (0.1)	
Nausea	16 (2.0)	14 (1.8)	2 (0.3)	
Neck pain	3 (0.4)		3 (0.4)	
Oropharyngeal pain	4 (0.5)	4 (0.5)		
Osteopenia	2 (0.3)	2 (0.3)		
Pain in extremity	7 (0.9)	3 (0.4)	4 (0.5)	

Preferred term	All, N (%)		Mild, N (%)		Moderate, N (%)		Severe, N (%)	
Paresthesia	2	(0.3)	2	(0.3)				
Pharyngitis streptococcal	2	(0.3)	2	(0.3)				
Plantar fasciitis	2	(0.3)	1	(0.1)	1	(0.1)		
Pneumonia	2	(0.3)			2	(0.3)		
Pruritus	5	(0.6)	3	(0.4)	2	(0.3)		
Rash	5	(0.6)	4	(0.5)	1	(0.1)		
Respiratory tract infection	2	(0.3)	1	(0.1)	1	(0.1)		
Sciatica	2	(0.3)	1	(0.1)	1	(0.1)		
Seasonal allergy	3	(0.4)	3	(0.4)				
Sinusitis	21	(2.7)	13	(1.7)	8	(1.0)		
Skin laceration	4	(0.5)	1	(0.1)	1	(0.1)	2	(0.3)
Somnolence	14	(1.8)	11	(1.4)	3	(0.4)		
Toothache	3	(0.4)	1	(0.1)	2	(0.3)		
Tooth infection	2	(0.3)	1	(0.1)	1	(0.1)		
Transient ischemic attack	2	(0.3)			1	(0.1)	1	(0.1)
Upper limb fracture	2	(0.3)			1	(0.1)	1	(0.1
Upper respiratory tract infection	2	(0.3)	2	(0.3)				
Urge incontinence	24	(3.1)	18	(2.3)	6	(0.8)		
Urinary incontinence	3	(0.4)	1	(0.1)	2	(0.3)		
Urinary retention	7	(0.9)	7	(0.9)				
Urinary tract infection	47	(6.0)	34	(4.3)	11	(1.4)	2	(0.3)
Urine odor abnormal	5	(0.6)	5	(0.6)				
Vaginal hemorrhage	2	(0.3)	2	(0.3)				
Vertigo	2	(0.3)	1	(0.1)	1	(0.1)		
Vision blurred	5	(0.6)	5	(0.6)				
Visual acuity reduced	3	(0.4)	1	(0.1)	2	(0.3)		
Visual impairment	2	(0.3)	1	(0.1)	1	(0.1)		
Vitamin D deficiency	2	(0.3)	2	(0.3)				
Vomiting	2	(0.3)	1	(0.1)	1	(0.1)		
Vulvovaginal mycotic infection	2	(0.3)	2	(0.3)				
Wrist fracture	3	(0.4)			3	(0.4)		

Source: CONTROL CSR

Table 4 CONTROL: Adverse Events in Two or More Subjects Associated with Discontinuation (N=785)

Preferred term	All		Mild		Moderate		Severe	
	N	%	N	%	N	%	N	%
Anxiety	2	(0.3)	1	(0.1)	1	(0.1)		
Application site erythema	4	(0.5)	4	(0.5)				
Application site irritation	54	(6.9)	50	(6.4)	4	(0.5)		
Application site pruritus	3	(0.4)	3	(0.4)				
Application site rash	3	(0.4)	3	(0.4)				
Application site reaction	8	(1.0)	7	(0.9)	1	(0.1)		
Back pain	2	(0.3)	1	(0.1)			1	(0.1)
Constipation	3	(0.4)	3	(0.4)				
Cystitis	3	(0.4)	1	(0.1)	2	(0.3)		
Dizziness	6	(0.8)	5	(0.6)	1	(0.1)		
Dry eye	2	(0.3)	2	(0.3)				
Dry mouth	6	(0.8)	6	(0.8)				
Dysuria	2	(0.3)	1	(0.1)	1	(0.1)		
Fatigue	2	(0.3)	2	(0.3)				
Flank pain	2	(0.3)	1	(0.1)	1	(0.1)		
Headache	2	(0.3)	1	(0.1)	1	(0.1)		
Hypersensitivity	4	(0.5)	3	(0.4)			1	(0.1)
Hypertension	2	(0.3)	1	(0.1)	1	(0.1)		
Insomnia	2	(0.3)	2	(0.3)				
Muscle spasms	2	(0.3)	1	(0.1)	1	(0.1)		
Nausea	3	(0.4)	2	(0.3)	1	(0.1)		
Pain in extremity	2	(0.3)	1	(0.1)	1	(0.1)		
Plantar fasciitis	2	(0.3)	1	(0.1)	1	(0.1)		
Somnolence	4	(0.5)	3	(0.4)	1	(0.1)		
Upper limb fracture	2	(0.3)			1	(0.1)	1	(0.1)
Urge incontinence	8	(1.0)	4	(0.5)	4	(0.5)		
Urinary tract infection	10	(1.3)	6	(0.8)	2	(0.3)	2	(0.3)

Source: CONTROL CSR

LISTING OF 80 SUBJECTS WHO HAD NEW SYMPTOM OR WORSENING BUT APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
10-0031	Began taking a diuretic (AE of water retention)	**Stopped use:** Subject had been managing her OAB symptoms for 3 years including doctor oversight and diagnosis. Subject experienced a new symptom of vaginal spotting and made an appointment with her doctor. During the visit her doctor noticed her ankles and feet were swollen. Her doctor diagnosed her with water retention and told her to stop using the patch.
10-0081	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe**: Early in study participation, Subject had an AE of application site mild irritation. Subject removed patch and changed its location. The problem resolved without the need for medication. The Subject applied one patch after onset of this irritation and then stopped patch use due to a worsening of application site irritation.
10-0096	Worsening urge incontinence	**Condition/worsening OAB/symptom occurred after stopping use:** According to Follow-up week 12 Subject interview, Subject ran out of patches and did not have a way to get to the Pharmacy to purchase more drug. Subject's OAB symptoms worsened after stopping patch.
10-0102	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe:** Subject experienced mild skin irritation throughout study participation. Subject reported that the irritation was not a problem until she started a new box. At that time the irritation symptoms worsened and she stopped patch use due to the worsening.
11-0019	UTI	**Talked to doctor and continued use:** Subject had been managing her OAB symptoms for 3 years including doctor oversight and diagnosis. After experiencing symptoms of increased urgency and dysuria, Subject made an appointment with her doctor. Subsequently, the subject was diagnosed with a UTI.

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		During the office visit the subject made her doctor aware of her study participation and patch use. Subject reported that the doctor did not tell her to stop her use of the patch.
11-0150	Pain or burning when urinating (AE of burning when urinating) Pelvic pain	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 6 months including doctor oversight and diagnosis. Subject experienced burning when urinating and made an appointment to see her doctor. Subject received treatment for symptoms and was instructed by her doctor to continue patch use. Subject ran out of patches and didn't have time to get more prior to the onset of AE (pelvic pain). Therefore, subject was not using the patch when her symptoms began. Subject's pelvic pain was diagnosed as an ovarian cyst, unrelated to patch use (history of ovarian cysts).
12-0032	Bladder infection	**Other (did not start treatment until bladder infection resolved):** The day of the enrollment visit, Subject felt that she was getting a bladder infection. She did not start study drug and instead made an appointment with her doctor the next day. Her doctor diagnosed her with a bladder infection. Subject started study drug after bladder infection had resolved.
12-0039	Worsening urge incontinence	**Other (made an appointment with urologist):** Subject had been managing her OAB symptoms for 2 years including doctor oversight and diagnosis. Subject made an appointment with her Urologist after noticing an increase in her urinary incontinence. Subject continued to use the patch and reported improvement of her symptoms at the follow-up week 12 Subject interview.
12-0056	Pain or burning when urinating (AE of dysuria)	**Symptom self-limited and resolved:** Five weeks after starting study drug, Subject reported dysuria. The AE was mild and self-resolved, lasting about 3 days without pharmaceutical intervention.

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
	Lower back pain unrelated to injury (AE of worsening back pain)	**Symptom was pre-existing:** Subject has suffered from spinal stenosis and curvature of the spine for 30 years. During study participation she experienced a worsening of her back pain. She saw her Chiropractor and took OTC Tylenol and ibuprofen for the pain. The AE was assessed as unlikely related to the patch by the study investigator.
12-0076	Worsening (AE of worsening of urinary urgency)	**Stopped use when symptom worsened/became severe:** Subject applied one patch after onset of AE (the day after the onset).
12-0077	Mild stomach ache (AE of stomach ache)	**Symptom self- limited and resolved:** Subject stopped patch use one day prior to onset of AE symptom. Subject's stomach pain resolved in 3 days without treatment. Subject resumed treatment eleven days after stopping patch use. Subject reported no additional experiences of stomach pain. AE was of short duration and appears to be unrelated to patch.
12-0085	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe:** Subject tried two patches and then stopped use due to skin irritation.
12-0086	Worsened (AE of worsening urge incontinence) Influenza (AE of influenza with symptom of stomach discomfort)	**Condition/worsening OAB/symptom occurred after stopping use:** Worsening occurred after Subject temporarily stopped use of the patch due to influenza symptoms (reported at Follow-up week 7). Subject restarted patch after flu resolved. Her urge incontinence continued to worsen and again she stopped use and talked with her doctor (reported at Follow-up week 12). **Talked to doctor/HCP and stopped use:** Subject stopped patch use and sought medical diagnosis and treatment for influenza (stomach ache).
12-0122	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe:** Subject stopped using the patch when symptoms worsened. Started at mild irritation at first patch and progressed to more severe irritation with last patch.
12-0136	Abdominal pain (AE of pelvic inflammatory disease)	**Talked to doctor/HCP and stopped use:** Sixteen days after starting drug, Subject experienced abdominal pain, high fever, and abdominal cramping. Subject sought

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		treatment at the E.R. and was subsequently diagnosed with pelvic inflammatory disease. Subject temporarily stopped study drug. This event was assessed by the study investigator as unlikely related to study drug.
	Fever/urinary tract infection UTI	**Talked to doctor/HCP and stopped use:** In both cases of UTI, Subject stopped use and was treated by doctor.
14-0028	Worsening urge incontinence	**Other (stopped use and restarted Rx medication):** Subject had been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Subject stopped use of patch when urge incontinence worsened. She then resumed previous prescription oral OAB medication which had worked in the past.
14-0034	Bladder infection	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 10 years including doctor oversight and diagnosis. Subject made and appointment with doctor, was treated, and was told to continue using the patch.
15-0014	Worsening of OAB Urinary tract infection	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Worsening of OAB was associated with, and symptomatic of, AE of UTI. **Talked to doctor and told to continue use:** Subject did not stop using the patch, but called doctor's office and got UTI treated
16-0002	Lower abdominal pain (AE of lower abdominal pain)	**Symptom self-limited and resolved:** Subject had been managing her OAB symptoms for 10 years. Subject reported waking up with mild pain in lower abdominal area. She stated that the pain is reoccurring in the mornings and once she gets up and does her exercises and takes a bath the pain resolves. She continued the use the patch throughout the study and did not report any further incidences of abdominal pain. The pain appears to be musculoskeletal and self-limited, therefore no medical reason to

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		stop or talk to doctor.
16-0014	Worsening of incontinence	**History of worsening OAB symptoms followed by improvement:** Subject had been managing her OAB symptoms for 6 years including doctor oversight and diagnosis. Subject has history of intermittent worsening. Worsening was followed by improvement. Intermittent worsening of incontinence is part of the variability of the underlying condition.
16-0026	Flank (side) pain Worsening (AE of worsening of frequency)	**Other (pre-existing condition and stopped use until resolved):** Subject had been managing her OAB symptoms for 10 years including doctor oversight and diagnosis. Prior to study participation Subject fell on right side and has experienced flank pain ("just under my ribs") off and on ever since. After starting study patch, the pain returned (7/17/2010) and subject stopped use and saw her doctor about the condition. The subject's flank pain resolved on 7/24/2010. On 7/25/2010 the subject applied a study patch and continued use until 8/14/2010 (last patch applied), at which time she permanently discontinued drug use. **Condition/worsening OAB/symptom occurred after stopping use:** Four weeks (9/14) after Subject stopped patch use she experienced a worsening of frequency, unlikely related to study drug as assessed by study physician.
16-0096	Lower back pain unrelated to injury	**Symptom was pre-existing**: Subject had been managing her OAB symptoms for 12 years including doctor oversight and diagnosis. Subject reported experiencing back pain on both sides of lower in the mornings. By the afternoon the pain had dissipated. The study physician assessed the event as unrelated to OAB condition and use of the patch.
16-0098	Allergic reaction to the patch (AE of application site allergic reaction)	**Talked to doctor/HCP and stopped use**; **stopped use when symptoms worsened/became severe:** Subject had been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Subject reported mild redness and itchiness at patch application site. Subject did not talk

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		to her doctor, but talked to her pharmacist who told her she was probably having an allergic reaction to the patch adhesive. Subject discontinued patch use permanently when symptoms became more bothersome.
16-0102	Worsened (not reported as an AE, because it was associated with, and symptomatic of, AE of UTI) UTI	**Talked to doctor and told to continue use**: Subject had an increase in her urinary urgency which made her think she had an infection. She saw her doctor and was diagnosed with a UTI. Her doctor told her to continue using the patch.
16-0107	Burning with urination	**Stopped Use:** Subject stopped patch and burning subsided. She did not restart the patch.
17-0060	Allergic reaction to patch (AE of application site allergic reaction) UTI	**Stopped use and talked to doctor:** For both application site allergic reaction and UTI Subject stopped patch use and saw her doctor.
17-0124	Pain or burning when urinating (AE of pain with urination)	**Symptom self-limited and resolved:** Pain was self-limited (lasted a couple of hours and then resolved completely). She was planning to see a physician.
19-0010	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped Use:** Subject tried different spots and then stopped patch use permanently when symptoms did not resolve.
19-0021	Urinary tract infection	**Talked to doctor/HCP and stopped use:** Subject had been managing her OAB symptoms for 30 years including doctor oversight and diagnosis. Subject reported a history of UTI's, and that she had another ecoli UTI start while using the patch. She saw her doctor and was treated. However, Subject decided on her own to stop using the patch because it was not working for her (no improvement in OAB symptoms).
19-0069	UTI	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 10 years including doctor oversight and diagnosis. Doctor found asymptomatic UTI on routine exam. Subject appropriately continued to use the patch since the UTI was not related to patch use and not a reason to stop using the patch.

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
19-0119	UTI	**Talked to doctor/HCP and stopped use:** Subject stopped using the patch and saw her doctor.
21-0062	Allergic reaction to patch (AE of application site allergic reaction)	**Stopped use when symptoms worsened/became severe:** Subject had been managing her OAB symptoms for 3 years including doctor oversight and diagnosis. Subject reported redness from use of the patch. Redness worsened with continued use and placement at various sites. After the application of 3 patches the subject discontinued drug permanently.
21-0094	UTI	**Talked to doctor and told to continue use:** Subject reported that she started to experience dysuria and because of her history of UTIs should make an appointment with her doctor. Subject saw her doctor, was treated, and was told to continue using the patch.
21-0152	Worsening (AE of worsening OAB symptoms)	**Stopped and talked to doctor:** Subject had been managing her OAB symptoms for 5 years including doctor oversight and diagnosis. Subject reported temporarily stopping patch use due to worsening of OAB symptoms. Subject restarted using patch and then discontinued permanently when OAB symptoms did not improve. According to the End Of Study interview, Subject reported talking to her doctor about her OAB symptoms.
22-0022	Bladder infection	**Talked to doctor and told to continue use**: Subject had been managing her OAB symptoms for 5 years including doctor oversight and diagnosis. Subject began feeling an increase of urgency and frequency with some dysuria. She went to an instacare clinic where she was diagnosed with and treated for a mild bladder infection. Subject continued drug use throughout the study.
22-0036	Lower abdominal pain (AE of lower abdominal pain)	**Talked to doctor/HCP and stopped use:** When pain did not resolve after one week, Subject stopped using the patch and sought

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		medical diagnosis.
22-0074	Worsening urge incontinence	**Talked to doctor/HCP and stopped use**: Subject applied one patch after onset of worsening and talked to her doctor.
23-0011	Worsening of OAB symptoms UTI	**Condition/worsening OAB/symptom occurred after stopping use:** Subject had been managing her OAB symptoms for 4 years including doctor oversight and diagnosis. Subject has a history of UTI and when she felt that her urgency was worsening she stopped use and made an appointment with her doctor. Subsequently she was diagnosed with a UTI.
23-0018	Worsening urgency	**Stopped use when symptoms worsen/became severe:** Subject had been managing her OAB symptoms for 12 years including doctor oversight and diagnosis. Subject was taking a prescription OAB medication prior to study participation. She discontinued her Rx medication and started the patch on 7/20/2010. She reports that her OAB symptoms worsened almost immediately. Subject discontinued patch use within 3 days due to this worsening.
23-0028	Urinary tract infection	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 35 years including doctor oversight and diagnosis. Subject saw doctor, who diagnosed and treated UTI, and instructed Subject to continue using the patch.
23-0036	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptoms worsen/became severe:** Subject had been managing her OAB symptoms for 39 years including doctor oversight and diagnosis. Subject stopped patch use when symptoms worsened, three days after onset of severe redness.
23-0042	Allergic reaction to the patch	**Stopped Use**: Subject stopped using the patch, but retried a month later, wearing one patch and then stopping.
23-0056	Lower back pain unrelated to injury	**Symptom self-limited and resolved:** Self-limited pain for a few hours when patch is applied each time. Not symptomatic of UTI.
23-0061	Worsened (AE of worsening urge incontinence)	**Stopped Use:** Subject talked to her doctor

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		and stopped use of the patch
	Blood in urine not related to menses	**Condition/worsening OAB/symptom occurred after stopping use**: Subject had already stopped patch use. In retrospect, Subject believed blood was related to menses from irregular birth control pill use. AE spontaneously resolved.
25-0002	Lower back pain unrelated to injury (AE of worsening lower back pain)	**Symptom was pre-existing:** Subject had been managing her OAB symptoms for 2 years including doctor oversight and diagnosis.
		Subject had a 6-month history of lower back pain at enrollment. She talked to doctor after starting use of the patch, and was told it was okay to use.
	Belly ache (AE of diarrhea)	**Symptom was self-limited and resolve:** Belly ache was reported as an accompanying symptom with AE of diarrhea. The belly ache was of short duration (1 day), and spontaneously resolved.
25-0008	Flank (side) pain (AE of flank pain on right side under ribs)	**Talked to doctor/HCP and stopped use:** Subject stopped patch use and saw a doctor, who determined that an ovarian mass was the cause of flank pain. The cause was not urinary and not related to study drug as assessed by the study physician.
26-0058	Lower back pain unrelated to injury	**Stopped Use:** Subject reported temporarily stopping patch use after experiencing lower back pain. She restarted the patch but discontinued patch use permanently after experiencing flank pain and realizing the association of the pain with the patch.
	Flank (side) pain (AE of right flank pain)	
26-0070	Liver or kidney disease (AE of elevated kidney function tests)	**Symptom was pre-existing:** Subject reported a 2 year history of Kidney disease. Subject was under a doctor's care for her condition
		This event was probably unrelated to patch use, as assessed by the study physician.
26-0087	Worsening urge incontinence	**Stopped use when symptom worsens/became severe:** Subject stopped use of patch when symptoms worsened.
	UTI	**Condition/worsening OAB/symptom occurred after stopping use:** UTI was identified by positive UA at pharmacy two weeks after last patch removal date. Subject denied having UTI symptoms, and follow-up from retirement home was negative.

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
26-0121	Lower abdominal pain (AE of lower abdominal pain)	**Talked to doctor and told to continue use**: Subject talked to doctor and followed doctor's advice to remove patches early (after three days instead of four).
26-0140	UTI	**Talked to doctor and told to continue use**: Diagnosis of UTI is not a reason to stop patch use. Subject was seen by a doctor and treated.
27-0003	Low back pain unrelated to injury (AE of lower back pain)	**Symptom self-limited and resolve:** Subject had been managing her OAB symptoms for 10 years including doctor oversight and diagnosis. Unrelated to study drug as assessed by the study physician, and of short duration (5 days). Subject had lower back pain upon waking in the morning and it resolved during the day.
27-0069	Pain or burning when urinating (AE of dysuria) Worsening urge incontinence	**Symptom self-limited and resolved:** Subject had symptoms of increased urgency, frequency, with some dysuria and thought she might be getting a UTI. Subject drank cranberry juice and symptoms resolved after 1-2 days.
29-0011	Pain or burning when urinating (AE of burning with urination)	**Symptom self-limited and resolved:** Self-limited burning with urination (2 days).
29-0024	Abdominal cramping	**Symptom self-limited and resolve:** AE described as 'like menstrual cramps', was short duration (3 days) and resolved spontaneously.
30-0039	Urinary tract infection	**Talked to doctor and told to continue use:** Subject had been managing her OAB symptoms for 3 years. At the enrollment visit the subject reported having cloudy urine for 1 year. Twenty-seven days after taking her first dose of study drug, Subject was seen by her nephrologist for a follow-up because of a history of renal insufficiency and recurrent UTI. Subject was diagnosed with an asymptomatic UTI (27 days after first dose of study drug). Subject discussed her patch use with her doctor and was told to continue using the patch.
30-0060	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe:** Subject stopped patch use when symptoms worsened, it started as mild but worsened with subsequent patch use.

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
30-0084	Unable to empty bladder completely (AE of urinary retention)	**Stopped to doctor and told to continue use:** Subject had been managing her OAB symptoms for 25 years including doctor oversight and diagnosis. Subject spoke to doctor and followed his advice to continue using the patch.
31-0008	Allergic reaction to the patch (AE of application site allergic reaction)	**Not an allergic reaction:** Subject had been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Subject reported mild application site pruritus and erythema, which lasted for 2-3 days. Subject used OTC antibiotic cream and the symptoms resolved. Subject continued to use the patch throughout the study with no reoccurrence of application site irritation. The AE was probably incorrectly recorded as allergic reaction, when it was really a localized skin irritation.). Therefore, this Subject is mitigated since mild application site irritation is not a reason to stop patch use and talk to a doctor.
31-0047	Worsening (AE of worsened OAB)	**Stopped use when symptom worsened/became severe:** Subject stopped patch use a short time after OAB symptoms worsened.
31-0062	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation) Worsening (AE of worsening of incontinence)	**Talked to doctor/HCP and stopped us:** Subject had been managing her OAB symptoms for 10 years including doctor oversight and diagnosis. Subject talked to doctor who told her to discontinue the patch, which she did. **Condition/worsening OAB/symptom occurred after stopping use:** AE onset was after Subject had already discontinued using the patch.
31-0087	UTI	**Talked to doctor and told to continue use**. Subject saw her doctor, who told her to continue use of the patch.
31-0090	Bladder infection	**Talked to doctor/HCP and stopped use:** Subject had been managing her OAB symptoms for 2 years including doctor oversight and diagnosis. Subject saw her doctor, and stopped using the patch as directed by her doctor.

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
32-0014	Bladder infection	**Talked to doctor and told to continue:** Subject had been managing her OAB symptoms for 30 years including doctor oversight and diagnosis. Subject reported that she has a history of bladder infections and recognized the symptoms immediately. She saw her doctor and was diagnosed and treated. She continued to use the patch and the symptoms resolved completely within a couple of day. Diagnosis of bladder infection is not a reason to stop patch use.
32-0062	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptom worsened/became severe:** Subject had been managing her OAB symptoms for 5 years including doctor oversight and diagnosis. Subject stopped patch use when symptoms worsened.
32-0089	Lower back pain unrelated to injury (AE of lower R back pain)	**Other (talked to doctor about unrelated condition**: Subject had been managing her OAB symptoms for 2 years including doctor oversight and diagnosis. Unrelated to patch use. Subject saw her doctor, who thought this pain was related to Lupus.
32-0095	UTI	**Talked to doctor and told to continue use:** Asymptomatic UTI found by doctor, who told Subject to continue patch use.
33-0040	Severe redness, itchiness, or blistering at the site of application (AE of application site severe irritation)	**Stopped use when symptoms worsened/became severe:** Subject stopped using the patch when symptoms worsened.
34-0047	Foul-smelling urine Urinary tract infection	**Symptom was pre-existing:** Subject stated she had this problem before starting patch use, and AE resolved when she drank more water. **Talked to doctor and continued use**: Diagnosis of UTI is not a reason to stop patch use. Subject saw her doctor and was treated.
34-0065	Colitis (AE described by subject as colitis, with pain in lower right quadrant that felt like pain she had before with a diagnosis of colitis)	**Symptom was pre-existing (self-limited):** Subject had been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Symptoms were self-limited and had previously occurred prior to using the patch.

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		AE was short duration (3 days) and resolved with self-treatment.
35-0040	Severe redness, itchiness, or blistering at the site of application (AE of application site severe redness)	**Stopped Use:** Subject had been managing her OAB symptoms for 8 months including doctor oversight and diagnosis. AE occurred with last patch, and Subject appropriately did not use any more patches.
35-0050	UTI	**Talked to doctor and told to continue use**: Subject had been managing her OAB symptoms for 3 years including doctor oversight and diagnosis. Diagnosis of UTI is not a reason to stop patch use. Subject saw her doctor and was treated. Doctor told her to continue patch use.
36-0008	Allergic reaction to the patch (AE of application site allergic reaction)	**Not an allergic reaction:** Subject reported a mild redness, rash, and itchiness after removal of patch. Subject washed the affected area with mild soap and water and then applied Lubriderm lotion. Subject continued to use the patch throughout the study with no reoccurrence of application site irritation. The AE was probably incorrectly recorded as allergic reaction, when it was really a localized skin irritation. Therefore, this Subject is mitigated since mild application site irritation is not a reason to stop patch use and talk to a doctor.
36-0009	UTI	**Other (self-treated):** Subject had been managing her OAB symptoms for 50 years including doctor oversight and diagnosis. Twelve days after application of first patch, Subject recognized UTI symptoms (bladder spasm as described by Subject). Subject self-diagnosed and self-treated, which she would have done regardless of patch use. Since UTI is not a reason to stop patch use, Subject continued to use patch throughout the study without a reoccurrence of UTI.
36-0048	Severe redness, itchiness, or blistering at the site of application (AE of application site skin irritation)	**Stopped use when symptom worsened/became severe:** AE was rated as mild site skin irritation. Subject stopped patch use when symptoms worsened.
37-0022	Worsening urge incontinence	**Stopped use when symptom worsened/became severe:** Subject had

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Subject Number	Primary Endpoint Factor(s) of Misuse	Rationale for Mitigation
		been managing her OAB symptoms for 1 year including doctor oversight and diagnosis. Subject stopped patch use when symptoms worsened.
37-0081	Allergic reaction to the patch (AE of allergic reaction)	**Stopped use when symptom worsened/became severe:** Subject stopped patch use when symptoms worsened.
37-0131	Abdominal cramping (AE of abdominal cramping)	**Symptom self-limited and resolved:** AE began on day new prescription for diuretic was started. AE was short duration (1 day), and no medical reason to stop use. Subject planned to talk to doctor before restarting patch use.
37-0140	UTI	**Talked to doctor/HCP and stopped use:** Although it is not necessary to stop patch use for UTI, Subject did stop patch use when she developed symptoms, saw her doctor and was treated.
37-0142	Urinary retention (AE of worsening urinary retention)	**Talked to doctor and continued use:** Subject has history of urinary retention and saw her urologist, who told her to continue using the patch. Subject later stopped patch use due to AE of application site – mild irritation when it became worse with each new patch.

APPENDIX 6 - 80 SUBJECTS IN CONTROL WITH NEW SYMPTOMS WHO APPROPRIATELY CONTINUED OXYTROL

MedDRA System Organ Class	Mild		Moderate		Severe		Total	
	AEs	%AE[a]	AEs	%AE	AEs	%AE	AEs	%AE
Total reported AEs = 975	732	75.1%	206	21.1%	37	3.8%	975	100.0%
Cardiac disorders	1	0.1%	1	0.1%	2	0.2%	4	0.4%
Ear and labyrinth disorders	3	0.3%	1	0.1%	0	0.0%	4	0.4%
Eye disorders	21	2.2%	11	1.1%	0	0.0%	32	3.3%
Gastrointestinal disorders	103	10.6%	15	1.5%	1	0.1%	119	12.2%
General disorders and administration site conditions	193	19.8%	11	1.1%	1	0.1%	205	21.0%
Hepatobiliary disorders	0	0.0%	0	0.0%	3	0.3%	3	0.3%
Immune system disorders	10	1.0%	1	0.1%	1	0.1%	12	1.2%
Infections and infestations	151	15.5%	55	5.6%	6	0.6%	212	21.7%
Injury, poisoning and procedural complications	9	0.9%	20	2.1%	8	0.8%	37	3.8%
Investigations	10	1.0%	0	0.0%	0	0.0%	10	1.0%
Metabolism and nutrition disorders	11	1.1%	3	0.3%	1	0.1%	15	1.5%
Musculoskeletal and connective tissue disorders	36	3.7%	32	3.3%	3	0.3%	71	7.3%
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5	0.5%	1	0.1%	1	0.1%	7	0.7%
Nervous system disorders	51	5.2%	17	1.7%	4	0.4%	72	7.4%
Psychiatric disorders	7	0.7%	8	0.8%	2	0.2%	17	1.7%
Renal and urinary disorders	55	5.6%	15	1.5%	0	0.0%	70	7.2%
Reproductive system and breast disorders	12	1.2%	4	0.4%	1	0.1%	17	1.7%
Respiratory, thoracic and mediastinal disorders	28	2.9%	2	0.2%	1	0.1%	31	3.2%
Skin and subcutaneous tissue disorders	17	1.7%	5	0.5%	1	0.1%	23	2.4%
Surgical and medical procedures	2	0.2%	0	0.0%	0	0.0%	2	0.2%
Vascular disorders	7	0.7%	4	0.4%	1	0.1%	12	1.2%

% AE = AEs/Total reported AEs(975)

Source: Data from CONTROL Clinical study report Table 14.12.25.

Findings for Secondary Endpoints Based upon Initial Classification

The CONTROL protocol specified that the original analysis of Secondary Endpoints 1, 3 and 5 were based upon CRF Recorded Data without any review for mitigating factors that could justify consumer behavior. FDA Guidances specify that review of all subject data is necessary to define correct consumer behavior. This appendix compares the findings from the initial analysis with those after reclassification for mitigating factors.

Secondary Endpoint 1

Secondary Endpoint 1 is the proportion of subjects who did not stop using Oxytrol after developing a new symptom referred to anywhere in OTC labeling or after symptoms worsened. The proportion was calculated by dividing the total number of subjects in these categories by the total number of subjects that used the Oxytrol patch at least once. Table 1 shows the differences in findings between the initial classification and that based upon reclassification for mitigating factors.

Table 1 The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Worsened - Users

Secondary Endpoint 1	Initial Classification (N=727)	Reclassification (N=727)
Total subjects who had no symptoms indicating they should stop use	598 (82.3%)	598 (82.3%)
Total subjects who had symptoms indicating they should stop use	129 (17.7%)	129 (17.7%)
Total subjects who correctly stopped use (pre-mitigation) or were medically acceptable (post-mitigation):	34 (4.7%)	106 (14.6%)
Developed a new symptom only	26 (3.6%)	78 (10.7%)
Condition worsened only	5 (0.7%)	17 (2.2%)
Developed new symptom and conditioned worsened	3 (0.4%)	11 (1.5%)
Total subjects who failed to stop use:	95 (13.1%)	23 (3.2%)
Developed a new symptom only	63 (8.7%)	11 (1.5%)
Condition worsened only	23 (3.0%)	11 (1.5%)
Developed new symptom and conditioned worsened	9 (1.2%)	1 (0.1%)
Total subjects who failed to stop use	95 (13.1%)	23 (3.2%)
95% CI (LL, UL)[a]	(10.7%, 15.7%)	(2.0%, 4.7%)

a Confidence intervals derived using SAS Frequency Procedure with the Binomial option.

Secondary Endpoint 3

Secondary Endpoint 3 was the proportion of subjects who did not stop using Oxytrol within two weeks after experiencing no improvement in their symptoms. Two reviewers (employed by the Sponsor) conducted a reclassification of Secondary Endpoint 3 independently from each other. If the reviewers agreed that the subject's behavior was acceptable, then the behavior was judged as correct.

Table 2 Secondary Endpoint 3 - The Proportion of Users Who Did Not Stop Use Within 2 Weeks After No Improvement[a] - Users

Secondary Endpoint 3	All Subjects Initial Classification	All Subjects Reclassification
Total subjects asked the question at least 2 weeks after their first application[b]	643	643
Subjects reporting improvement	456 (70.9%)	456 (70.9%)
Subjects reporting no improvement (stayed the same or worsened)	187 (29.1%)	187 (29.1%)
Total subjects with no improvement who correctly stopped use	42 (6.5%)	116 (18.0%)
Total subjects with no improvement who failed to stop use	145 (22.6%)	71 (11.0%)
95% CI (LL, UL)[c]	(19.4%, 26.0%)	(8.7%, 13.7%)

[a] A subject is considered to have had no improvement if they provided a response to Question 2 in the 3-week follow-up interview that indicated their symptoms "Stayed the same" or "Worsened" after 2-weeks of verified use. Due to the wording of the question, this information can only be obtained from the week-3 follow-up interview.

[b] Of the N=727 subjects in the User Population, N=690 had used the product by the date of the first follow-up interview and N=643 had been using the product for a full 2-weeks.

[c] Confidence intervals derived using SAS Frequency Procedure with the Binomial option.

At the FDA's request, an analysis combining the Primary Endpoint and Secondary Endpoint 3 was also conducted to show the proportion of subjects who did not stop use when they either developed a new symptom referred to anywhere in the labeling or when their condition did not improve (worsened or stayed the same) with the addition of abdominal and pelvic pain. Table 5 shows findings from the initial analysis and then those after reclassification based upon the presence of mitigating factors.

Secondary Endpoint 5 was analyzed based on pre- and post-mitigation assessments but the post-mitigation analysis includes all subject data and is a better reflection of the subject's overall behavior. Table 3 presents the proportion of subjects who misused the Oxytrol patch. Of the subjects who incorrectly used the patch, more favorable results were seen when the data were analyzed post-mitigation versus pre-mitigation (21.2%; 95% CI: 18.3%, 24.4% versus 51.7%; 95% CI 47.9%, 55.4. When evaluating the data post-mitigation, the majority of subjects correctly used (≤ 4 days and no simultaneous use) the Oxytrol patch (78.8%; 95% CI: 75.6%, 81.7%).

In addition, assessment of individual patch use showed that subjects used patches correctly 84.9% of the time pre-mitigation (95% CI 84.1, 85.7%).

Table 3 Proportion of Subjects Who Misused the Patch (Incorrect Duration of Use and/or Simultaneous Use) – Users

Secondary Endpoint 5	Patches Used (N=7874)[a]	Total Subjects Pre-Mitigation (N=727)[a]	Total Subjects Post-Mitigation (N=727)[a,b]
Incorrect use (> 4 days or simultaneous use)	1180 (15.0%)	370 (51.7%)	152 (21.2%)
95% CI (LL, UL)[c]	(14.2%, 15.8%)	(47.9%, 55.4%)	(18.3%, 24.4%)
Correct use (≤ 4 days, no simultaneous use)	6694 (84.9%)	346 (48.3%)	564 (78.8%)
95% CI (LL, UL)[c]	(84.1%, 85.7%)	(44.6%, 52.1%)	(75.6%, 81.7%)

a Some subjects with verified use had missing patch use entries.
b Confidence intervals derived using SAS Univariate Procedure with the Binomial option.
Source: Table 14-11-28, CONTROL CSR.

Table 4, a subgroup analysis of Secondary Endpoint 5, evaluates the proportion of subjects who misused the Oxytrol patch due to applications greater than 4 days. When the data of subjects who incorrectly used the Oxytrol patch were evaluated prior to the mitigation assessment, 46.5% (95% CI: 42.8%, 50.2%) of subjects misused the patch. However, when the data were evaluated after the mitigation assessment, the percentage of subjects who misused the Oxytrol patch greater than 4 days decreased to 21.6% (21.6%; 95% CI: 18.7%, 24.8%).

Table 4 Proportion of Subjects Who Misused the Patch With Applications > 4 Days – Users

Secondary Endpoint 5 – Duration of Use Only	Patches Used (N=7874)[a]	Total Subjects Pre-Mitigation (N=727)[a]	Total Subjects Post-Mitigation (N=727)[a,b]
Incorrect use (> 4 days)	935 (11.9%)	333 (46.5%)	155 (21.6%)
95% CI (LL, UL)[c]	(11.2%, 12.6%)	(42.8%, 50.2%)	(18.7%, 24.8%)
Correct use (≤ 4 days)	6939 (88.0%)	383 (53.5%)	561 (78.4%)
95% CI (LL, UL)[c]	(87.3%, 88.7%)	(49.8%, 57.2%)	(75.2%, 81.3%)

a Some subjects with verified use had missing patch use entries.
b See Statistical Analysis Plan for mitigation rules.
c Confidence intervals derived using SAS Univariate Procedure with the Binomial option.
Source: Table 14-11-29, CONTROL CSR.

Table 5 Combined Primary Endpoint and Secondary Endpoint 3: The Proportion of Subjects Who Did Not Stop Use When They Either Developed a New Symptom Referred to Anywhere in the Labeling or When Their Condition Did Not Improve (Worsened or Stayed the Same) With the Addition of Abdominal and Pelvic Pain - Users

Primary Endpoint[a] Combined with Secondary Endpoint 3[a]	**Initial Classification (N=727)[a,b]**	**Reclassification (N=727)[a]**
Total subjects who met either the criteria of the Primary Endpoint or Secondary Endpoint 3[c]	276 (38.0%)	Not applicable
Developed a new symptom	115 (15.8%)	Not applicable
OAB condition worsened	40 (5.5%)	Not applicable
OAB condition stayed the same at Follow-up Visit 3	174 (23.9%)	Not applicable
Total subjects who correctly stopped use (pre-mitigation) or were medically acceptable (post-mitigation)[c]	**57 (7.8%)**	187 (25.7%)
Developed a new symptom	27 (3.7%)	93 (12.8%)
OAB condition worsened	8 (1.1%)	25 (3.4%)
OAB condition stayed the same at Follow-up Visit 3	34 (4.7%)	105 (14.4%)
Total subjects who failed to stop use[c]	**219 (30.1%)**	89 (12.2%)
Developed a new symptom	88 (12.1%)	22 (3.0%)
OAB condition worsened	32 (4.4%)	15 (2.1%)
OAB condition stayed the same at Follow-up Visit 3	140 (19.3%)	69 (9.5%)
Total subjects who failed to stop use	**219 (30.1%)**	89 (12.2%)
95% CI (LL, UL)[d]	(26.8%, 33.6%)	(9.9%, 14.8%)

a For Secondary Endpoint 3 (SE3), users who did not stop use within 2-weeks after no improvement (stayed the same or worsened) analysis only includes subjects who were asked the question about improvement at least 2-weeks after their first application. Of the N=727 subjects in the User Population, N=690 had used the product by the date of the first follow-up interview and N=643 had been using the product for a full 2-weeks.

b Includes N=12 subjects only presenting with complaints of abdominal or pelvic pain (includes subjects who mentioned abdominal and pelvic pain in narratives of potentially related adverse experiences.

c Subjects are counted either as meeting the criteria of both the PE and SE3 or not meeting one of the endpoints. Under each group the subject will be counted in the row of each specific criterion. Counts of subjects who met or did not meet the specific criteria shown above will not match the counts displayed in the individual endpoint tables since a subject might have met one endpoint but not the other. In addition, a mitigation assessment for the PE will take priority if a subject does not meet the criteria for both endpoints. Note: One subject, who is counted in the total counts of misusers, is not included in any specific row because she was incorrect for all three criteria.

d Confidence intervals derived using SAS Frequency Procedure with the Binomial option.

CL2010-08: STUDY SYNOPSIS

Title of Study: Characterizing the Incidence of Initial Presentation of Urinary Frequency in Women Diagnosed with Urinary Tract Infection, Diabetes Mellitus or Bladder Cancer

Study Sponsor: Schering-Plough HealthCare Products, Inc.[1]

Study Center(s): This study was conducted at four sites:

- Cerner Health Facts®
- University of Utah Health System
- Geisinger Health System
- Henry Ford Health System

Study Dates: August 01, 2010 through November 01, 2010

Objective

This was a retrospective electronic medical record extraction and analysis. The primary objective was to evaluate the incidence of female patients, aged 18 to 85 years, diagnosed with urinary tract infection (UTI), diabetes mellitus (DM), or bladder cancer (BC), who presented with an initial primary complaint or reason for visit consistent with signs or symptoms of overactive bladder (OAB).

Secondary objectives included assessing if the primary complaint was consistent with urinary frequency, urgency, or incontinence; and categorizing all primary complaints that led to the incident diagnosis of UTI, DM, or BC.

Study Methodology

This was a 4-site retrospective medical chart extraction and analysis conducted in female patients aged 18 to 85 years. At each study site, potential medical records were identified through ICD-9 diagnostic codes for UTI, DM, or BC, and were screened for additional inclusion and exclusion criteria. Patient records meeting study requirements were placed into a potential cohort pool, and a random stratified sample was drawn from the pool for data abstraction and analysis. Data were collected through retrieval from patient records, either from an electronic medical record (EMR) and/or physical medical charts. Abstraction of data from the medical records utilized a standardized data collection tool of pre-specified variables and

[1] On April 1, 2011, Schering-Plough HealthCare Products, Inc. changed its legal entity name to MSD Consumer Care, Inc., operating under the trade name Merck Consumer Care (MCC).

data definitions. Study sites were assigned to deliver a specific number of completed patient records for each diagnosis.

Number of Medical Records (Planned and Analyzed)

A total of 1,550 records of female patients with a primary diagnosis of UTI (n=600), DM (n=600), or BC (n=350) by ICD-9 code in the primary diagnosis field were planned; 1,599 such records were available for the final analysis consisting of UTI (n=706), DM (n=609), and BC (n=284).

Main Criteria for Inclusion

Females were required to be from 18 to 85 years old on the initial date of primary diagnosis for UTI, DM, or BC, and had to meet other protocol-specified inclusion and exclusion criteria before their medical charts were selected for extraction. Patients were excluded if they had a diagnosis of pregnancy in the 6 months before or within 30 days following the diagnosis of UTI, DM, or BC. Patients were also excluded if they had a diagnosis of malignant neoplasm in the 6 months prior to the diagnosis of UTI, DM, or BC, and patients were excluded without an observable treatment period of at least 6 months prior to the initial diagnosis of UTI, DM, or BC.

Criteria for Evaluation

The primary purpose of the analyses was to determine the prevalence of primary complaints or reasons for visit that were consistent with pre-defined criteria for the signs and symptoms of OAB. Secondary criteria were assessed for urinary urgency, frequency, or incontinence; and non-OAB symptoms were also assessed and categorized.

The “primary complaint/reason for visit” data field was evaluated and scored by two independent clinicians for assignment into either consistent or not consistent with pre-defined symptoms of OAB, in addition to scoring symptoms of urinary frequency, urgency or incontinence. When the scores of the two reviewers differed, consensus was attempted through discussion.

Statistical Methods

The primary analyses for this study were descriptive. All analyses were performed using SAS v9.2 (SAS Institute, Inc., Cary, NC). Summary statistics for continuous variables included the mean, median, and standard deviation; categorical variables were summarized with absolute numbers and proportions/percentages. A two-sided 95% confidence interval was determined for the point estimates of the percentage of patients with a primary presenting complaint consistent with OAB for the UTI, DM, and BC cohorts. For comparisons of variables that were proportions, the chi-squared test was employed. In cases where the population was too small for chi-

square, a Fisher's exact test was used. For continuous variables such as age, the Student's *t* test for normally distributed variables and the Wilcoxon two-sample test with the two-sided *t* approximation for skewed approximations were employed. All comparisons were considered significant at $P<0.05$.

Missing values for continuous and categorical variables were recorded as unknown.

The Kappa test for inter-rater agreement was used to test the degree of agreement between the clinicians scoring the patient primary complaint.

A stratified analysis of the point estimate for OAB symptoms was conducted to investigate if differences in OAB symptoms as a primary complaint differed across study site locations, patient demographics, physician specialty, or place of service for the three disease cohorts.

Results

A total of 1,599 female patient records were available for analysis of the primary endpoint of presenting with an initial primary complaint or reason for visit consistent with signs or symptoms of OAB. The point prevalence of OAB in each of the three groups was as follows: UTI, 20 of 706 patients or 2.83% (95% CI 1.78% - 4.41%); DM, 9 of 609 patients or 1.48% (95% CI 0.72% - 2.89%); and BC, 21 of 284 patients or 7.39% (95% CI 4.75% - 11.24%).

Urinary Tract Infection

The ages of the patients ranged from 18 to 85 years, with a mean (median) age of 45.3 (44) years. The year of initial diagnosis ranged from 2004 to 2010, with a slightly greater proportion of the patients coming from the years 2004 to 2006. Approximately two thirds of the patients received the initial diagnosis in the outpatient environment, with approximately one third being diagnosed during an emergency department encounter. The point estimate (95% CI) for patients with an initial presenting complaint or reason for visit consistent with OAB was 2.83% (1.78% - 4.41%). The most frequent non-OAB primary complaints in the UTI group included lower quadrant/back/abdominal/leg pain (33%), dysuria (28%), and general malaise/fatigue/pain (17%). Urinary frequency was observed in 10% of those with UTI. A higher proportion of patients age 40 or older (3.9%) had a primary complaint that was consistent with OAB compared with those younger than 40 (1.6%). Overall, a small portion of the UTI population was diagnosed during a follow-up for a pre-existing medical condition or routine visit/labs.

Diabetes Mellitus

The ages of the patients ranged from 18 to 85 years, with a mean (median) age of 53.4 (53) years. The year of initial diagnosis ranged from 2004 to 2010, with a relatively even distribution of patients across the time period. Approximately 84% of

the patients received the initial diagnosis in the outpatient environment, with approximately 6% being diagnosed during an emergency department encounter and 5% during an inpatient encounter. The point estimate (95% CI) for patients with an initial presenting complaint or reason for visit consistent with OAB was 1.48% (0.72% - 2.89%). The most common primary complaint/reason for visit in the DM group (in 49%) was a follow-up for a pre existing medical condition or routine visit/labs. The other frequent non-OAB primary complaints in the DM group included lower quadrant/back/abdominal/leg pain (19%), general malaise/fatigue/pain (16%), and infection related (11%). While the majority (80%) of patients diagnosed with DM were older than 40 years, symptoms consistent with OAB were more frequent in those younger than 40 (2.6%) than in those age 40 or older (1.2%). It is interesting to note that 25 patients diagnosed with DM presented with a reason for visit that included a high blood glucose reading from a blood glucose meter of a relative, friend, or testing location.

Bladder Cancer

The ages of the patients ranged from 18 to 85 years, with a mean (median) age of 66.8 (69) years. The year of initial diagnosis ranged from 2004 to 2010, with a relatively even distribution of patients across the time period. Approximately 75% of the patients received the initial diagnosis in the outpatient environment, with approximately 11% being diagnosed during an emergency department encounter. The point estimate (95% CI) for patients with an initial presenting complaint or reason for visit consistent with OAB was 7.39% (4.75% - 11.24%). The most common primary complaint/reason for visit in the BC group (in 49%) was hematuria. The other frequent non-OAB primary complaint/reason for visit in the BC group included: follow-up for a pre-existing medical condition or routine visit/labs (29%), lower quadrant/back/abdominal/leg pain (18%), and dysuria (12%). While 90% of the patients diagnosed with BC were older than 40, no patients younger than 40 diagnosed with BC had a primary complaint consistent with OAB.

Conclusions and Discussion

This retrospective medical chart abstraction of 1,599 female patients receiving an initial diagnosis of UTI (n=706), DM (n=609), or BC (n=284) suggests a low overall incidence of presenting with a primary complaint or reason for visit for a medical encounter consistent with signs or symptoms of OAB. For UTI and DM, the incidence of presenting with symptoms consistent with OAB was estimated to be less than 5%; and for BC, the 95% CI ranged from approximately 5% to 11%.

In UTI, the reason for seeking medical help appears to be strongly symptom driven, with lower quadrant pain, dysuria, and general malaise making up more than 75% of the primary complaints seen in this population. While urinary urgency, frequency, or incontinence was seen in more than 10% of the UTI group, the occurrence of pain readily rules out OAB. The UTI group was the youngest population. The UTI

population also presented in the emergency department much more frequently than the DM or BC groups.

Patients diagnosed with DM had the lowest incidence of symptoms consistent with OAB. Almost half the patients diagnosed with DM were being seen for routine care, which is not surprising given the generally asymptomatic nature of the disease in its early stages. Those patients presenting with specific symptoms typically presented with symptoms that were not urinary related. It was somewhat surprising to see that more than a third of the patients diagnosed with DM were younger than 40 years.

Bladder cancer had the highest incidence of primary complaint or reason for visit consistent with the definition of OAB and had the highest incidence of incontinence, but had rates of urinary urgency and frequency that were generally in line with what was seen in the UTI group. The higher incidence of OAB was likely due to a much lower frequency of dysuria compared with the UTI group, and the majority (12 of 21 cases) of BC occurred in the aged 65 and older population, which may represent a group that does not become as alarmed with back or flank pain as younger patients.

Overall, it appears that the incidence of female patients presenting to a health care professional with symptoms meeting the definition of OAB represent a small minority of patients that are ultimately diagnosed with UTI, DM, or BC.

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

Product of Switzerland

Oxytrol® FOR WOMEN

Oxytrol® FOR WOMEN

New!

Full Prescription Strength
OXYBUTYNIN 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

0 00000 00000 0

Oxytrol® FOR WOMEN

Drug Facts

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

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

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New!
Full Prescription Strength
OXYBUTYNIN 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)	Purpose
Oxybutynin transdermal system 3.9 mg/day	overactive bladder treatment

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 <u>any</u> 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 redness 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.

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

Product of Switzerland

OXYTROL®
Oxybutynin Transdermal System

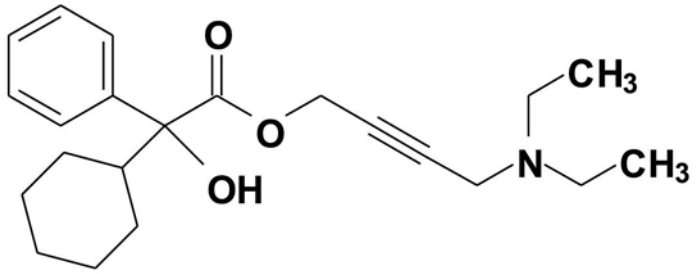
DESCRIPTION

OXYTROL, oxybutynin transdermal system, is designed to deliver oxybutynin continuously and consistently over a 3- to 4-day interval after application to intact skin.

OXYTROL is available as a 39 cm^2 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 (interindividual 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 $C_{22}H_{31}NO_3$. Its structural formula is:



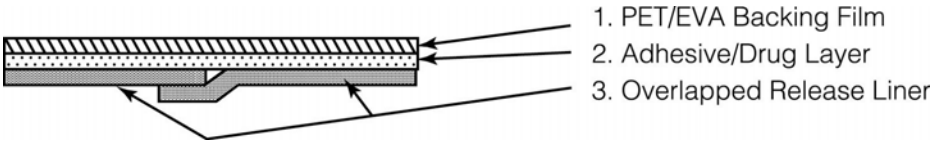
Oxybutynin is a white powder with a molecular weight of 357. It is soluble in alcohol, but relatively insoluble in water.

Transdermal System Components

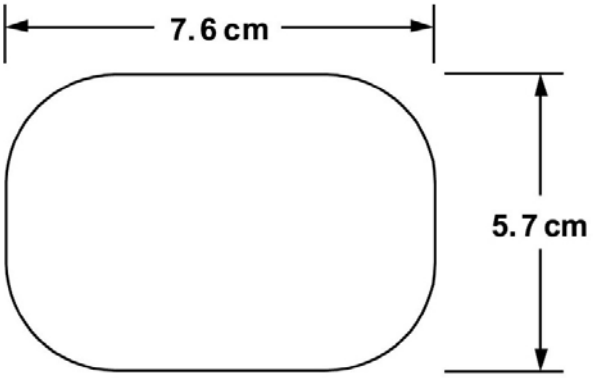
OXYTROL is a matrix-type transdermal system composed of three layers as illustrated in Figure 1 below. Layer 1 (Backing Film) is a thin flexible polyester/ethylene-vinyl acetate film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2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



CLINICAL PHARMACOLOGY

The free base form of oxybutynin is pharmacologically equivalent to oxybutynin hydrochloride. Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with conditions 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 thus decreases urinary urgency and the frequency of both incontinence episodes and voluntary urination.

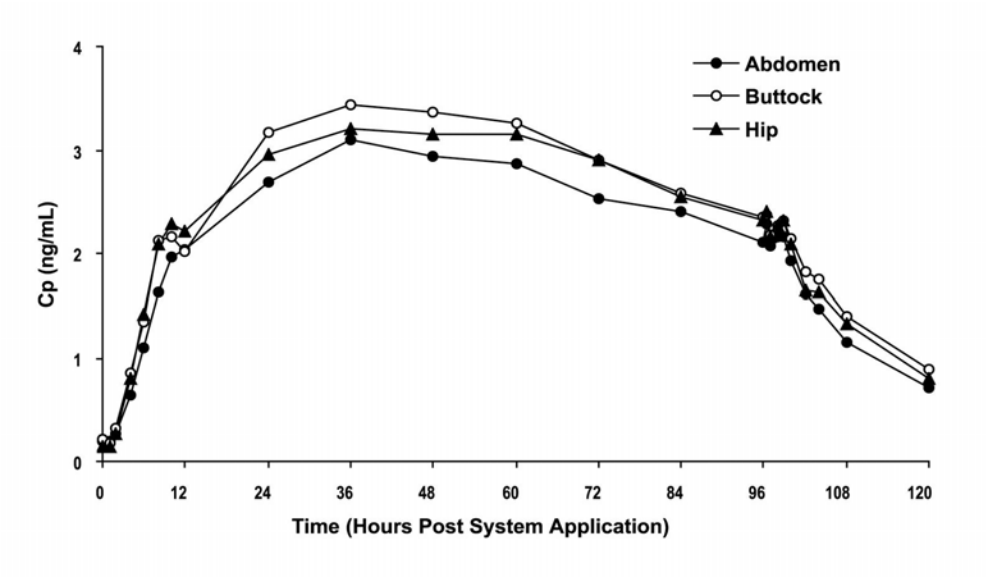
Oxybutynin is a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly in the R-isomer. The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in vitro* studies.

Pharmacokinetics

Absorption

Oxybutynin is transported across intact skin and into the systemic circulation by passive diffusion across the stratum corneum. The average daily dose of oxybutynin absorbed from the 39 cm^2 **OXYTROL** system is 3.9 mg. The average (SD) nominal dose, 0.10 (0.02) mg oxybutynin per cm^2 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 concentration increases for approximately 24 to 48 hours, reaching average maximum concentrations of 3 to 4 ng/mL. Thereafter, steady concentrations are maintained for up to 96 hours. Absorption of oxybutynin is bioequivalent when **OXYTROL** is applied to the abdomen, buttocks, or hip. Average plasma concentrations measured during a 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 1 provides a summary of pharmacokinetic parameters of oxybutynin in healthy volunteers after single and multiple applications of **OXYTROL**.

Figure 3: Average (SEM) steady-state oxybutynin and N-desethyloxybutynin plasma concentrations (Cp) measured in 13 healthy volunteers following the second transdermal system application in a multiple-dose, randomized, crossover study.

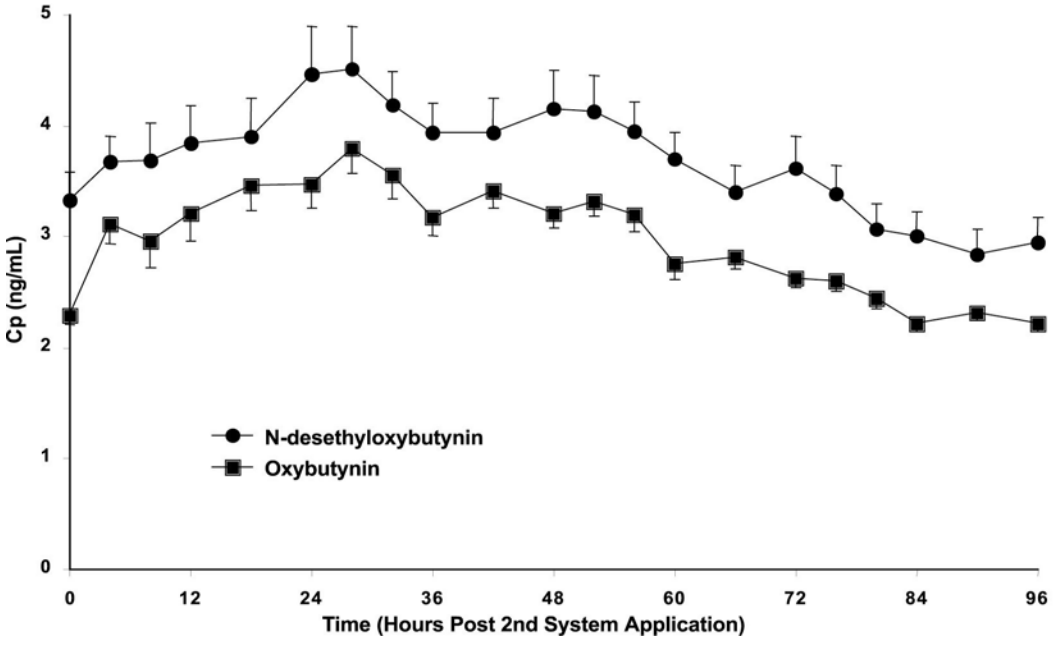


Table 1: Mean (SD) oxybutynin pharmacokinetic parameters from single and multiple dose studies in healthy men and women volunteers after application of **OXYTROL** on the abdomen.

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

[1] T_{max} given as median
[2] AUC_{inf}
[3] AUC_{0-96}
[4] AUC_{0-84}

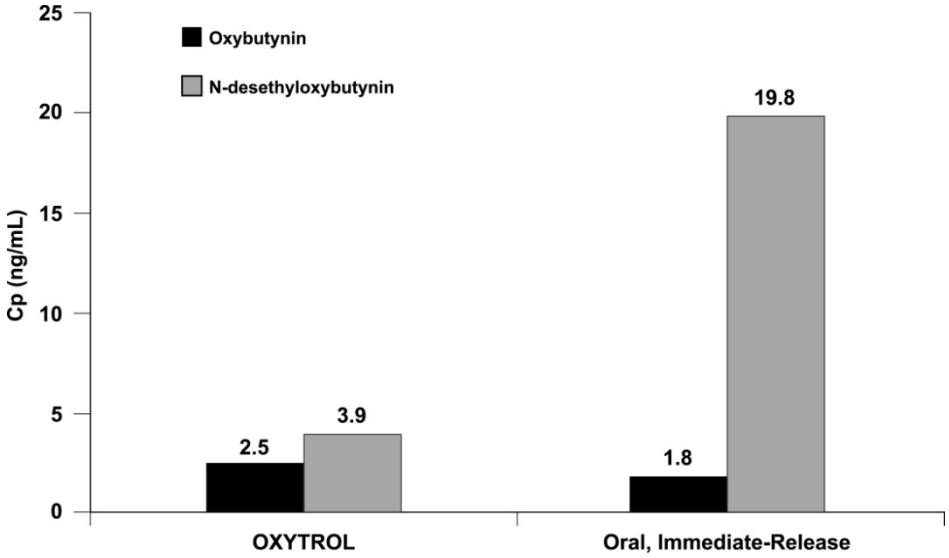
Distribution
Oxybutynin is widely distributed in body tissues following systemic absorption. The volume of distribution was estimated to be 193 L after intravenous administration of 5 mg oxybutynin chloride.

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

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

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

Figure 4: Average plasma concentrations (Cp) 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.

Special Populations

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

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

Gender: There were no significant differences in the pharmacokinetics of oxybutynin in healthy male and female volunteers following application of **OXYTROL**.

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

Renal Insufficiency: There is no experience with the use of **OXYTROL** in patients with renal insufficiency.

Hepatic Insufficiency: There is no experience with the use of **OXYTROL** in patients with hepatic insufficiency.

Drug-Drug Interactions: See **PRECAUTIONS: Drug Interactions.**

Adhesion

Adhesion was periodically evaluated during the Phase 3 studies. Of the 4,746 **OXYTROL** evaluations in the Phase 3 trials, 20 (0.4%) were observed at clinic visits to have become completely detached and 35 (0.7%) became partially detached during routine clinic use. Similar to the pharmacokinetic studies, > 98% of the systems evaluated in the Phase 3 studies were assessed as being ≥ 75% attached and thus would be expected to perform as anticipated.

Clinical Studies

The efficacy and safety of **OXYTROL** were evaluated in patients with urge urinary incontinence in two Phase 3 controlled studies and one open-label extension. Study 1 was a Phase 3, placebo controlled study, comparing the safety and efficacy of **OXYTROL** at dose levels of 1.3, 2.6, and 3.9 mg/day to placebo in 520 patients. Open-label treatment was available for patients completing the study. Study 2 was a Phase 3 study, comparing the safety and efficacy of **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 **OXYTROL** doses of 1.3, 2.6, and 3.9 mg/day with matching placebo. An open-label, dose titration treatment extension allowed continued treatment for up to an additional 40 weeks for patients completing the double-blind period. The majority of patients were Caucasian (91%) and female (92%) with a mean age of 61 years (range, 20 to 88 years). Entry criteria required that patients have urge or mixed incontinence (with a predominance of urge), urge incontinence episodes of ≥ 10 per week, and ≥ 8 micturitions per day. The patient's medical history and a urinary diary during the treatment-free baseline period confirmed the diagnosis of urge incontinence. Approximately 80% of patients had no prior pharmacological treatment for incontinence. Reductions in weekly incontinence episodes, urinary frequency, and urinary void volume between placebo and active treatment groups are summarized in Table 2.

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

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

*Comparison significant if $p < 0.05$
**Comparison significant if $p \leq 0.0167$

Study 2 was a randomized, double-blind, double-dummy, study of **OXYTROL** 3.9 mg/day versus active and placebo controls conducted in 361 patients. The 12-week double-blind treatment included an **OXYTROL** dose of 3.9 mg/day, an active comparator, and placebo. The majority of patients were Caucasian (95%) and female (93%) with a mean age of 64 years (range, 18 to 89 years). Entry criteria required that all patients have urge or mixed incontinence (with a predominance of urge) and had achieved a beneficial response from the anticholinergic treatment they were using at the time of study entry. The average duration of prior pharmacological treatment was greater than 2 years. The patient's medical history and a urinary diary during the treatment-free baseline period confirmed the diagnosis of urge incontinence. Reductions in daily incontinence episodes, urinary frequency, and urinary void volume between placebo and active treatment groups are summarized in Table 3.

Table 3: Mean and median change from baseline to end of treatment (Week 12 or last observation carried forward) in incontinence episodes, urinary frequency, and urinary void volume in patients treated with **OXYTROL** 3.9 mg/day or placebo for 12 weeks (Study 2).

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

OXYTROL is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who are at risk for these conditions. **OXYTROL** is also contraindicated in patients who have demonstrated hypersensitivity to oxybutynin or other components of the product.

WARNINGS

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

PRECAUTIONS

General

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

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

Gastrointestinal Disorders: **OXYTROL** should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention (see **CONTRAINDICATIONS**).

OXYTROL, like other anticholinergic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis. **OXYTROL** should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis.

Information for Patients

Patients should be informed that heat prostration (fever and heat stroke due to decreased sweating) can occur when anticholinergics such as oxybutynin are used in a hot environment. Because anticholinergic agents such as oxybutynin may produce drowsiness (somnolence), dizziness or blurred vision, patients should be advised to exercise caution. Patients should be informed that alcohol may enhance the drowsiness caused by anticholinergic agents such as oxybutynin.

Patients should be informed that angioedema has been reported with oral oxybutynin use. Patients should be advised to promptly discontinue oxybutynin therapy and seek immediate medical attention if they experience symptoms consistent with angioedema.

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. Details on use of the system are explained in the patient information leaflet that should be dispensed with the product.

Drug Interactions

The concomitant use of oxybutynin with other anticholinergic drugs or with other agents that produce dry mouth, constipation, somnolence, and/or other anticholinergic-like effects may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Pharmacokinetic studies have not been performed with patients concomitantly receiving cytochrome P450 enzyme inhibitors, such as antimycotic agents (e.g. ketoconazole, itraconazole, and miconazole) or macrolide antibiotics (e.g. erythromycin and clarithromycin). No specific drug-drug interaction studies have been performed with **OXYTROL**.

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.

Pregnancy: Teratogenic Effects

Pregnancy Category B

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus.

Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride. The safety of **OXYTROL** administration to women who are or who may become pregnant has not been established. Therefore, **OXYTROL** should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Nursing Mothers
It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **OXYTROL** is administered to a nursing woman.

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

Geriatric Use
Of the total number of patients in the clinical studies of **OXYTROL**, 49% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, *Special Populations: Geriatric***).

ADVERSE REACTIONS
The safety of **OXYTROL** was evaluated in a total of 417 patients who participated in two Phase 3 clinical efficacy and safety studies and an open-label extension. Additional safety information was collected in Phase 1 and Phase 2 trials. In the two pivotal studies, a total of 246 patients received **OXYTROL** during the 12-week treatment periods. A total of 411 patients entered the open-label extension and of those, 65 patients and 52 patients received **OXYTROL** for at least 24 weeks and at least 36 weeks, respectively.

No deaths were reported during treatment. No serious adverse events related to treatment were reported.

Adverse events reported in the pivotal trials are summarized in Tables 4 and 5 below.

Table 4: Number (%) of adverse events occurring in ≥ 2% of **OXYTROL**-treated patients and greater in **OXYTROL** group than in placebo group (Study 1).

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

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

Table 5: Number (%) of adverse events occurring in ≥ 2% of **OXYTROL**-treated patients and greater in **OXYTROL** group than in placebo group (Study 2).

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

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

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

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

Treatment-related adverse events that resulted in discontinuation were reported by 11.2% of **OXYTROL**-treated patients in Study 1 and 10.7% of **OXYTROL**-treated patients in Study 2. Most of these were secondary to application site reaction. In the two pivotal studies, no patient discontinued **OXYTROL** treatment due to dry mouth.

In the open-label extension, the most common treatment-related adverse events were: application site pruritus, application site erythema and dry mouth.

Post Marketing Surveillance

The following event has been reported in association with **OXYTROL** use in clinical practice: dizziness. Because spontaneously reported events are from worldwide post marketing experiences, the frequency of events and the role of **OXYTROL** in their causation cannot be reliably determined.

OVERDOSAGE

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 symptomatic treatment.

DOSAGE AND ADMINISTRATION

OXYTROL should be applied to dry, intact skin on the abdomen, hip, or buttock. A new application site should be selected with each new system to avoid re-application to the same site within 7 days.

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

HOW SUPPLIED

OXYTROL 3.9 mg/day (oxybutynin transdermal system). Each 39 cm^2 system imprinted with **OXYTROL** 3.9 mg/day contains 36 mg 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 25°C (77°F); excursions permitted to 15-30°C (59-86°F). 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.

Rx only

A subsidiary of Watson Pharmaceuticals, Inc.
Corona, CA 92880 USA

Revised: January 2011

U.S. Patent Nos. 5,601,839; 5,834,010; and 7,179,483

200357-02

Information for the Patient
OXYTROL®Oxybutynin Transdermal System

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

What is OXYTROL?

OXYTROL is a transdermal system (skin patch) to treat overactive bladder. It delivers the active ingredient, oxybutynin, through your skin and into your bloodstream. Overactive bladder makes it hard to control when you urinate (pass water). Overactive bladder can make you urinate more often (increased frequency) or make you feel the need to urinate often (urgency). Overactive bladder can also lead to accidental urine loss (leaking or wetting oneself).

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.

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.
- **Pregnancy or breastfeeding.** Tell your doctor if you are pregnant or breastfeeding. OXYTROL may not be right for you.
- **Allergy to oxybutynin or the inactive ingredients in OXYTROL.** If you need to know the inactive ingredients, ask your doctor or pharmacist. If you have allergies to medical tape products or other skin patches, tell your doctor.

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

- Liver disease
- Kidney disease
- Bladder obstruction (blockage)
- Gastrointestinal obstruction (blockage in the digestive system)

- Ulcerative colitis (inflamed bowels)
- Myasthenia gravis (nerve weakness)
- Gastric reflux disease or esophagitis (inflamed esophagus, the tube between your mouth and stomach)

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

What should I avoid while using OXYTROL?
Do not expose the patch to sunlight. Therefore, wear it under clothing.

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

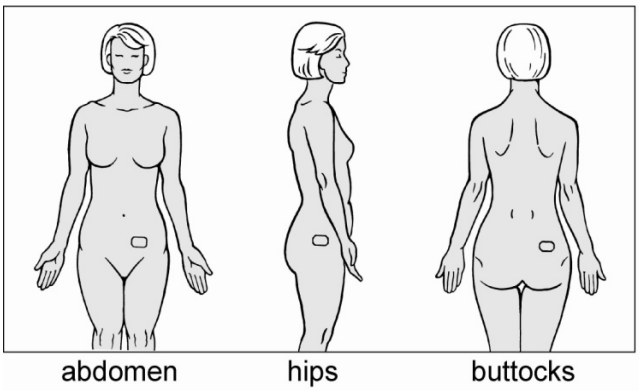
Oxybutynin may cause sleepiness or blurred vision, so be careful when driving or operating machinery. In addition, sleepiness may be increased by drinking alcohol (beer, wine or hard liquor).

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

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

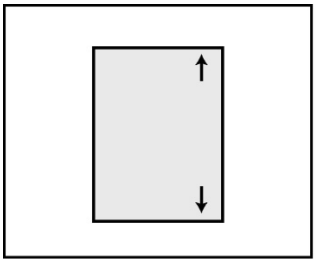
These are not all the side effects of OXYTROL. For a complete list, ask your doctor or pharmacist.

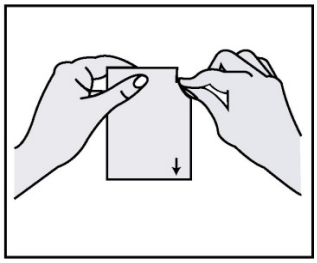
How should I use OXYTROL?
Put on a new patch of OXYTROL 2 times a week (every 3 to 4 days) according to your doctor’s instructions. Wear the patch all the time until it is time to apply a new one. Wear only 1 patch of OXYTROL at a time. Try to change the patch on the same 2 days each week. Your package of OXYTROL has a calendar checklist printed on the back to help you remember your schedule. Mark the schedule you plan to follow. Always change OXYTROL on the 2 days of the week you mark on the calendar.



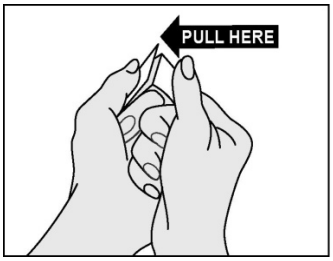
Put the patch on a clean, dry, and smooth (fold-free) area of skin on your abdomen (stomach area), hips or buttocks (as shown in the picture). Avoid your waistline area, since tight clothing may rub against the patch. The areas you choose should not be oily, damaged (cut or scraped), irritated (rashes)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

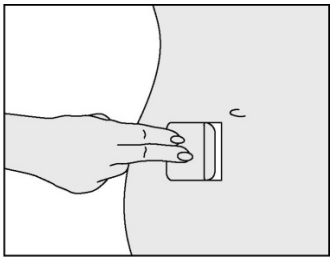
When you put on a new patch, use a different area of skin from the most recent patch site. You may find it useful to change the site from one side of your body to the other. Do not use the same area for the patch for at least 1 week. You may wish to try different locations when using OXYTROL to find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



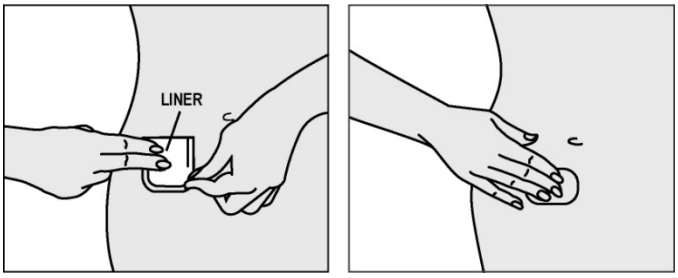


Each patch is sealed in its own protective pouch. When you are ready to put on the OXYTROL patch, tear open the pouch and remove the patch. Apply the patch to your skin right away. Do not keep or store the patch outside the sealed pouch.





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



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

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

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

When changing OXYTROL, remove the old patch slowly and carefully to avoid damaging the skin. Once off, fold the patch in half with the sticky sides together. **Since the patch will still contain some oxybutynin, throw it away so that it cannot be accidentally worn or swallowed by another person, especially a child, or a pet.**

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

Store at room temperature, 25°C (77°F). Temporary storage between 15 and 30°C (59 to 86°F) is also permitted. Keep OXYTROL and all medications in a safe, secure place and out of the reach of children.

General advice about OXYTROL

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not give OXYTROL to other people, even if they have the same symptoms you have. It may harm them.

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

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