

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202211s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	5-Dec-2012
From	Lesley-Anne Furlong
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	202-211
Supplement#	
Applicant	Merck Consumer Care
Date of Submission	26-Mar-2012
PDUFA Goal Date	26-Jan-2013
Proposed Proprietary Name / Established (USAN) names	Oxytrol for Women/oxybutynin
Dosage forms / Strength	Transdermal system/3.9 mg per 24 hours
Proposed Indication(s)	<p>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:</p> <ul style="list-style-type: none"> ○ 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)
Recommended:	<p><i>Approval contingent on</i></p> <ul style="list-style-type: none"> ● <i>Final agreement on labeling</i> ● <i>Satisfactory final inspection reports for the manufacturing and testing sites</i> ● <i>Satisfactory resolution of proposal for acceptance criteria for the presence of (b) (4)</i>

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1. Introduction

This is a summary review of an application for a partial prescription to over-the-counter switch for oxybutynin transdermal system. If approved, the product will be the first over-the-counter (OTC) drug therapy for overactive bladder (OAB) in the United States. The prescription product is approved for men and women; the applicant has proposed a “for women” OTC label to obviate concerns about men with undiagnosed prostate disease using the product and developing urinary retention. For simplicity, I refer to oxybutynin transdermal system as the oxybutynin TDS or the TDS in this review.

2. Background

Overactive bladder is a symptomatic and chronic condition that occurs in adults and is especially common among older adults. The symptoms of OAB include urinary incontinence, urgency, and frequency. OAB adversely impacts quality of life by causing embarrassment, sleep deprivation, and social limitations. The symptoms overlap and may co-exist with other conditions, such as diabetes, urinary tract infections, pregnancy, prostate disease, and stress incontinence. Treatments for overactive bladder include lifestyle changes, behavioral therapy, and drug therapy. FDA-approved drug therapies include anticholinergic drugs like oxybutynin and the adrenergic agonist mirabegron.

Oxybutynin and other anticholinergic drugs for OAB have modest efficacy and the expected anticholinergic adverse effects, for example, dry mouth, constipation, blurred vision, somnolence, and dizziness. According to prescription labeling, the most common adverse effects reported for the oxybutynin TDS were application site reactions, reported in over 25% of subjects.

The oxybutynin TDS was approved in Feb 2003 under the brand name Oxytrol (NDA 21351). The active ingredient has been available in oral tablets for the same indication since 1998. In addition to the oxybutynin TDS, the Orange Book currently lists oxybutynin tablets (NDA 20897), syrups (six ANDAs), and transdermal gels (NDA 22204 and NDA 202513).

The OTC development program was carried out under IND 74288. A detailed review of the regulatory history can be found in Dr. Raffaelli’s clinical review. Briefly:

- A preIND meeting held on 16-Apr-2007. The proposed consumer program and label were discussed. Concerns about the diagnosis in men who might miss prostate cancer were aired.
- General Correspondence 26-Mar-2008, providing FDA comments related to a protocol for a label comprehension study and revised label. The label at this point excluded men.

- End-of-Phase 2 meeting held on 13-Oct-2009 to discuss the further development of Oxytrol as an OTC product. FDA raised concerns about use by pregnant women, diabetics, or men. There was discussion about the issues of masking infection or bladder cancer. An actual use study was discussed.

To support Oxytrol's development for OTC use, the applicant has performed a series of consumer studies, including label comprehension studies (LCSs), self-selection studies (SSSs), and an actual use study (AUS). These include

- Protocol 82023: Pilot LCS
- Protocol 92062: LCS of enhanced pregnancy warning
- Protocol 92099: LCS of diabetes warning
- Protocol 92101: LCS among 65 and older women
- Protocol 10053: LCS among women with diabetes risk
- Protocol 10053: pivotal LCS among female OAB sufferers
- Protocol CL2008-19: Pilot SSS
- Protocol 92061: SSS in men
- Protocol 10054: SSS in pregnant women
- CONTROL Actual Use Study

Additionally, the applicant provides a summary of the safety profile from clinical trials and postmarketing data derived from spontaneous reports, a summary of adverse events (AEs) reported in a phase 4 study (MATRIX) conducted by Watson Pharmaceuticals, the prescription NDA holder, and a review of safety topics of special interest.

Because the indication is new to OTC labeling, a meeting of the Nonprescription Drug Advisory Committee was held on Nov. 9, 2012 to discuss the application.

In preparing this summary review, I have considered the applicant's submission, the discussion at the advisory committee meeting, and the following primary FDA reviews:

- Provision of Pharmacovigilance Data (Dr. Carolyn Volpe, Office of Surveillance and Epidemiology (OSE))
- Proprietary Name review (James Schlick (OSE))
- Drug Use review (Dr. Patty Greene (OSE))
- Clinical Inspection Summary review (Dr. Sharon Gershon of the Office of Scientific Investigations (OSI))
- Pharmacology/Toxicology review (Dr. Xinguang Li, Division of Nonprescription Clinical Evaluation (DNCE))
- Label, Labeling and Package review (James Schlick (OSE))
- Social Science review of label comprehension and self-selection studies (Barbara Cohen (DNCE))
- ONDQA Biopharmaceutics Review (Dr. Tapash Ghosh)
- Clinical review of the postmarketing data and actual use study (Dr. Ryan Raffaelli (DNCE))
- Statistical review (Dr. Yunfan Deng)

- Clinical review of prescription data (slide presentation to Advisory Committee by Dr. Donald McNellis, Division of Reproductive and Urologic Products (DRUP)). The clinical review from DRUP was not finalized when this review was completed.
- CMC review (Dr. Sheldon Markofsky, ONDQA)
- Dr. Ysern's review of proposed labeling (Division of Nonprescription Regulation Development (DNRD))

3. CMC/Device

The ONDQA biopharmaceutics team recommended approval from a biopharmaceutics point of view.

The CMC team has recommended a complete response for the following issues:

- Inadequate acceptance criteria for the presence of (b) (4)
- Labels and labeling do not have the required information
- An overall "Pending" recommendation has been issued for the manufacturing and testing sites by the Office of Compliance on 23-Oct-2012

The proposed OTC TDS is (b) (4) as the currently marketed Oxytrol except for

- The outermost (b) (4) layer of pouching material has been changed from (b) (4) (b) (4) layer to (b) (4). The pouching material that contacts the TDS is unchanged. The CMC reviewer found the applicant's submission adequate to support the use of the new pouching material.
- New manufacturing equipment to meet anticipated OTC market demands. The CMC and ONDQA reviewer found the information to support the manufacturing changes was acceptable. The change in equipment had no impact on the bioavailability of the drug product.

The transdermal system has three layers: a translucent backing film, an adhesive matrix containing the oxybutynin, and a liner that is removed before applying to the skin. Each system measures 7.6 cm by 5.7 cm and is imprinted with OXYTROL 3.9 mg/day. The systems are packed individually in heat sealed pouches. Each system contains oxybutynin 36 mg. Oxybutynin delivery over the four-day wear period is approximately 3.9 mg/day.

Labeling has been provided for 1-count, 4-count, 10-count, and 14-count cartons. This corresponds to 4-day, 16-day, 40-day, and 56-day treatment courses, respectively.

The CMC review states that the applicant has provided sufficient information to assure identify, strength, and purity of the drug product.

The original application requested a (b) (4); however, the CMC team identified a problem with (b) (4) during the review. (b) (4) The CMC team recommended a two-year shelf life until the (b) (4) issues can be adequately assessed and controlled.

Storage instructions on OTC labeling are the same as storage instructions on prescription labeling:

- Store between 20 to 25 degrees centigrade
- Protect from moisture and humidity
- Do not store outside the sealed pouch

4. Nonclinical Pharmacology/Toxicology

Dr. Li recommended approval of the NDA from a Pharmacology/Toxicology (P/T) perspective, based on “the previous human use experience for oxybutynin compounds, the agency’s previous review of the nonclinical information on the prescription product, as well as the lack of novel significant nonclinical toxicity findings identified during the current review.”

Dr. Li reviewed the prior P/T findings and noted that a chronic dermal toxicity study in animals and a dermal carcinogenicity bioassay were not conducted by the current or previous applicant. In evaluating this gap, the P/T team considered: 1) neither oxybutynin nor its main metabolite have structures that are similar to any of the compounds commonly associated with genotoxicity or carcinogenicity; 2) all genotoxicity studies were negative; 3) oral carcinogenicity studies were negative; 4) the administration sites of the product will be rotated among abdomen, hip, or buttocks; 5) oral oxybutynin and transdermal oxybutynin have been in clinical use for over 30 years and 10 years, respectively, and no signal has been identified related to dermal carcinogenicity. Therefore, the P/T review concluded that “the overall dermal carcinogenicity potential of the proposed product is considered to be low from a nonclinical perspective.”

The clinical data related to carcinogenicity are overall reassuring. Although OAB is a chronic condition, the duration of use of Oxytrol is limited: the mean duration of a treatment episode is two months, and less than 1% of users have treatment episodes lasting longer than one year. (See further details related to use in Section 7.) FDA’s Division of Pharmacovigilance (DPV) performed a search of the FDA’s Adverse Event Reporting System (AERS) for skin cancer (26-Feb-2003 through 6-Jun-2012). No skin cancers were reported. A review of the literature did not reveal a signal for dermal carcinogenicity. Although a data mining study¹ did detect several cases of Merkel cell cancer in patients who had been exposed to oxybutynin, the route of administration was unknown, and the authors did not view the cases as a signal. The generally short-term nature of use and the negative literature search were reassuring.

The Division Director for the Division of Nonprescription Clinical Evaluation and the Division Director for the Division of Dermatology and Dental Products (DDDP) met to discuss the totality of the data. The Director of DDDP had reviewed the relevant documents and, in that conversation, recommended that there was no need for preclinical dermal carcinogenicity data for the oxybutynin TDS.

¹ Friedman GD, et al. Screening pharmaceuticals for possible carcinogenic effects: initial positive results for drugs not previously screened. *Cancer Causes Control*. 2009 Dec; 20(10):1821 Review 20:1821-35

Prescription labeling describes Oxytrol as pregnancy category B: animal studies have not shown a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category B drugs are accepted in the OTC marketplace. The clinical reviewer searched AERS postmarketing reports for exposure to oxybutynin using query terms within MedDRA's Pregnancy and Neonatal Topics; he did not detect a signal from pregnancy exposures to oxybutynin. The applicant has proposed to label "if pregnant or breastfeeding, ask a health professional before use." This is acceptable text to capture the pregnancy information on OTC labeling.

5. Clinical Pharmacology/Biopharmaceutics

There was no new clinical pharmacology/biopharmaceutics information in the submission. The following summary comes from prescription labeling.

Oxybutynin is pharmacologically active, and it has an active metabolite, N-desethyloxybutynin (NDEO), which is pharmacologically similar to oxybutynin in vitro. The average daily dose of oxybutynin from the TDS is 3.9 mg. Following application of the first TDS, plasma concentrations increase for 24 to 48 hours, reaching maximum concentrations of 3 to 4 ng/mL and remaining steady for up to 96 hours. Absorption is bioequivalent whether applied to abdomen, buttocks, or hip. Steady state conditions are reached during the application of the second system. Oxybutynin is metabolized by the cytochrome P450 enzyme systems, particularly CYP3A4. The half-lives of oxybutynin and NDEO are approximately 7 to 8 hours. Comparison of a 96-hour application of the oxybutynin TDS to a single 5 mg oral dose of oxybutynin shows a 1.4-fold higher plasma concentration of oxybutynin for the TDS and a five-fold higher concentration of NDEO for oral oxybutynin. Rx labeling indicates similar PK in geriatric and younger subjects, no clinically significant gender- or race-based differences, and no experience with pediatric subjects or subjects with renal or hepatic insufficiency.

Labeling states that no drug-drug interaction (DDI) studies have been performed; however, the clinical reviewer found an article reporting a DDI study of oral oxybutynin and itraconazole, which is a strong CYP 3A4 inhibitor. In this study, concomitant therapy increased oxybutynin C_{max} and AUC two-fold; exposure to NDEO was not affected.

Comment: Concomitant use of a strong CYP3A4 inhibitor could increase the serum concentration of oxybutynin; increased exposure could increase the incidence or severity of anticholinergic effects.

The incidence or severity of anticholinergic effects may also be higher in the presence of other anticholinergic drugs.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Oxybutynin TDS shows modest efficacy in treating the symptoms of overactive bladder. Drug use data and the literature support that some users experience a meaningful benefit; however, most users do not use the TDS long-term.

There are no new efficacy data in this submission. Efficacy was established for prescription approval by showing a decrease in the number of incontinence episodes, with supportive data showing a decrease in the number of daily urinations and an increase in urinary void volumes. A summary of the efficacy findings from clinical trials follows.

Two Phase 3, randomized, double-blind, placebo-controlled clinical trials enrolled subjects with urge or mixed incontinence. Both trials used the change from baseline in number of incontinence episodes as the primary efficacy variable. Subjects in both trials were primarily female and Caucasian, with a mean age in the sixties.

In the first pivotal trial (Trial O99009), when compared with placebo, users of the oxybutynin TDS had a mean, placebo-subtracted decrease in:

1. number of weekly incontinence episodes by 4 episodes (from a baseline of 37.7 in the placebo group, and 34.3 in active group),
2. number of daily urinations by 1 (from a baseline of 12.3 in the placebo group and 11.8 in the active group)
3. urinary void volume by 20.5 cc² (approximately 1 tablespoon)

In the second pivotal trial (Trial O00011), when compared with placebo, Oxytrol showed a mean, placebo-subtracted decrease in:

1. daily incontinence episodes by 1 episode (from a baseline of 5 in placebo group, and 4.7 in the active group),
2. number of daily urinations by 1 (from a baseline of 12.3 in the placebo group and 12.4 in the active group)
3. urinary void volume by 18 cc (approximately 1 tablespoon)

Both trials had similar overall findings. The changes were statistically significant at the $p < 0.05$ level except for the change in daily urinations in the second study. In both trials, efficacy was demonstrated at the first on-treatment visit, which occurred at week 3 in the first trial and week 2 in the second trial.

² In women without detrusor overactivity, 20 cc represents less than 5% of bladder capacity. See Pfisterer MH, et al. Parameters of bladder function in pre-, peri-, and postmenopausal continent women without detrusor overactivity. *Neurourol Urodyn* 2007; 26(3):356-61

Comment: The proposed labeling recommends that consumers stop use and ask a doctor if symptoms do not improve after 2 weeks of use. This is acceptable as the clinical trial data support effectiveness by 2 weeks.

Although the mean changes produced by Oxytrol are small, some users experience changes that are meaningful to them. A recent systematic review³ of randomized controlled trials of drugs used for urgency incontinence concluded that the drugs showed similar small benefit. For oxybutynin, among 992 women, 11% more women in the active treatment group compared with the placebo groups achieved continence; among 1244 women, 21% more women in the active treatment group compared with the placebo group achieved a 50% reduction in incontinence episodes, which was defined as a clinically important improvement. The authors also examined quality-of-life data from validated scales. Based on the one study that met their criteria for quality-of-life assessment, transdermal oxybutynin neither improved quality of life nor resulted in treatment satisfaction when compared with placebo. According to the authors, about 20% of women who try Oxytrol will experience a clinically important benefit and 80% will not.

Despite the chronic nature of OAB, most patients do not appear to use Oxytrol long-term. FDA's Office of Surveillance and Epidemiology (OSE) provided a drug use review using nationally estimated prescription and patient data from 2003 through 2011. A total of 82.5% of users were female; 75% of the female users had 1 to 2 treatment episodes during the study period 2003-2011. The mean and median duration of treatment episodes per female patient were about two months and one month, respectively. Only 1% of patients had treatment episodes that lasted longer than one year. Findings were similar for men. The mean age of users was 65.1 years old for women and 67.5 years old for men.

The findings of the OSE review are consistent with Watson's Annual Report dated 27-Apr-2012 (filed under NDA 21351). During the reporting period Mar 2011-Feb 2012, a total of (b) (4) oxybutynin TDSs were distributed in the United States. During the same period, an estimated 126,408 patients were exposed to Oxytrol in the United States. These estimates are based on the number of new prescriptions written during the reporting period. The average number of TDSs per patient was 12, and 12 TDSs provides up to 48 days of treatment.

Comment: The efficacy of the oxybutynin TDS is modest. Drug use data support that most patients use the TDS no longer than a few months, suggesting that they make their own benefit risk assessment and find the TDS wanting. A minority of patients use the TDS long-term despite the chronic nature of their OAB symptoms.

8. Safety

Analysis of the applicant's submission did not reveal any unexpected safety findings. The most common adverse effect associated with the use of the TDS is local skin irritation. Other

³ Shamlivan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women: a systematic review. *Ann Intern Med.* 2012 Jun 19;156(12):861-74.

adverse effects caused by the TDS are likely related to its anticholinergic effects. Some users will experience dry mouth, constipation, dizziness, blurry vision, or sleepiness.

A clinically important but uncommonly reported safety issue is the potential for central nervous system (CNS) effects. A recent FDA evaluation of sporadic postmarketing reports of CNS-related AEs for anticholinergic OAB drugs resulted in upgraded warning language on Rx labeling (Oct 2012). CNS effects might be a special problem for consumers who use drugs that delay the metabolism of oxybutynin or that act at the same antimuscarinic receptors. The most vulnerable people are older consumers, as they may be on many drugs, have cognitive issues at baseline, and be at particular risk from dizziness and other CNS effects because of osteoporosis, anticoagulation, or other medical factors.

The safety database provided by the applicant for Oxytrol includes:

- Clinical trial data from the prescription NDA, including exposure of 663 patients and 83 healthy volunteers to one or more applications of Oxytrol.
- The applicant's CONTROL study, an actual use trial to assess appropriate use and safety by women who purchase and use Oxytrol in an over-the-counter use setting. A total of 785 women used at least one dose of Oxytrol.
- A summary of the post-marketing safety information from product launch to Feb 25 2011, with an estimated 270,000 patient-years of U.S. use and over 130,800 patient-years of foreign use. This included a review of the literature, a review of postmarketing safety from the AERS, WHO Vigibase, and AAPCC databases, and a summary of previously submitted periodic safety updates (U.S. PADERs and European PSURs).
- Watson Pharmaceuticals MATRIX study, a community-based, open-label phase 4 study which evaluated use of Oxytrol for up to 6 months in 2,881 enrolled adult patients with overactive bladder.
- A review of safety topics of special interest.

Except for some of the clinical trial data generated before the approval of prescription Oxytrol, the safety data are uncontrolled.

The reader is referred to the primary clinical review for a detailed review of the safety data. The following review is a summary.

8.1 Safety Findings in Preapproval Clinical Trials

The safety issues identified during preapproval clinical trials included skin tolerability and anticholinergic side effects, such as dry mouth and constipation.

The clinical trial database consisted of 19 trials that exposed 683 OAB patients and 83 healthy volunteers to oxybutynin TDS for periods from 1 to 428 days. The average exposure was 150 days. No deaths occurred during the clinical trials. Thirty-seven subjects experienced 47 serious adverse events (SAEs), none of which were considered related to Oxytrol.

Table 1. Summary of Adverse Events Seen in >1% of Subjects in the Phase 3 Trials

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

Source: Dr. McNellis' presentation at Advisory Committee Meeting (9-Nov-12)

Prescription labeling contains precautions and warnings that are anticholinergic drug class effects; this language is not based on specific safety signals seen with Oxytrol during clinical trials. The oxybutynin TDS is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, or hypersensitivity to the product. Angioedema has been reported with oral oxybutynin use. Labeling advises caution in patients with hepatic or renal impairment, bladder outflow obstruction, gastrointestinal obstructive disorder, disorders affecting gastrointestinal motility, or myasthenia gravis; labeling also advises caution in patients who are taking drugs, such as bisphosphonates, that can cause or exacerbate esophagitis. Labeling notes that heat prostration, drowsiness, dizziness, or blurred vision may occur, and alcohol may enhance drowsiness.

In the clinical trials leading to prescription approval, 49% of subjects were 65 and over. No overall differences in safety or effectiveness were observed between older and younger subjects.

8.2 CONTROL Actual Use Study

The CONTROL study was an open-label, single arm, multicenter actual use study (AUS) under simulated OTC conditions. The study provides uncontrolled safety data from women who were relying on an OTC label quite similar to the one proposed by the applicant for marketing. A total of 785 U.S. women who were concerned about their bladder symptoms purchased oxybutynin TDS and used it for up to 12 weeks. Although adherence to labeling was far from perfect, the study did not detect serious adverse events that resulted from inattention to labeling.

Interested women purchased TDSs in cartons containing 4 TDSs (equal to 16 days of TDS therapy) at one of 26 pharmacy sites. The pharmacist was available to answer questions but did not volunteer guidance. The pharmacist took a medical and demographic history. Subjects who reported glaucoma, pregnancy, breastfeeding, allergy to oxybutynin, hematuria, back pain/flank pain, and fever/chills with dysuria, foul-smelling urine, or cloudy urine were

excluded from the use phase. Subjects with other labeling ineligibilities were allowed to purchase. These other labeling ineligibilities could include symptoms, diagnoses, or use of other medication that should have led the subject either not to use or to seek medical advice first.

Subjects recorded the use of the product in a medication diary and had telephone interviews at 3, 7, and 12 weeks. Subjects could purchase up to 24 boxes (96 TDSs), which was adequate to detect any overuse that might occur. At Week 12, a urinalysis was performed. The end-of-study (EOS) interview explored reasons for various types of misuse.

A total of 1069 subjects decided to purchase the drug; 839 (78.5%) had some labeling ineligibility. Most (87.1%), however, had OAB symptoms for at least 3 months.

Except for 27 subjects with excluded medical conditions, subjects with labeled ineligibilities were permitted to purchase and use the drug. Of the 27 subjects who were not permitted to purchase the drug for medical reasons, four had narrow-angle glaucoma, 13 had blood in the urine, 5 were breastfeeding, 4 had a known allergy to oxybutynin, and 3 had symptoms of UTI (some had multiple exclusions). The remaining subjects who were not excluded for administrative reasons (n=187) were allowed to purchase and use the drug.

Although exclusions were minimal, they were enough to exclude 27 subjects who made a purchase decision. The follow-up on those excluded for medical reasons is limited; follow-up diagnoses included UTI (n=2), pre-diabetes, Type 2 diabetes, recurrent kidney stones, and irregular menstrual bleeding. Among the subjects with hematuria, several indicated they were under a doctor's care, one stated "the blood has stopped," one noted blood in June but "not at the moment, one thought "the blood was barely there," etc. Only one subject reported not seeing the statement on the package.

Comments: The large number of subjects who decided to purchase the drug despite one or more labeling ineligibilities suggests that subjects either did not read or chose not to comply with labeling. The label comprehension and self-selection studies reviewed in Section 12.1 Label Comprehension Studies and Self-Selection Studies, support that subjects can understand the labeling when asked to read it. The primary reviewer explored this issue in some detail. It did not appear that safety issues arose as a result of the ineligibilities.

There was some consumer misunderstanding of "urinary retention" leading to many more consumers thinking they had this condition than actually had an objective diagnosis. The proposed labeling related to urinary retention has been modified by adding the words "if you have been told by a doctor you have."

A total of 785 subjects reported using the TDS; 727 of 785 were defined as verified users based on diary confirmation of use.

The study met its primary endpoint, which was the proportion of verified users who did not stop use when they developed new or worsening symptoms over all verified users. The prespecified threshold was < 5%. The misuse by some subjects was mitigated based on

evaluation of interview responses. The post-mitigation result was 3.4% (25 of 727 verified users). The primary reviewer evaluated all mitigations and agreed with all but two. Counting those two subjects as misusers changes the misuse rate to 3.6%, which does not affect the conclusion that the study met its pre-specified endpoint. Subgroup analysis of the primary endpoint by race, age, or literacy did not reveal marked differences (proportions ranged from 1.1% for low literate consumers to 6% for non-white consumers). The statistical reviewer assessed the calculations of the endpoints for the actual use study and did not identify any statistical issues to preclude approval.

The primary clinical reviewer explored the proportion of users who had new or worsening symptoms and failed to stop use over all users who had new or worsening symptoms. Post-mitigation, 17.7% of subjects fell into this group (25 of 141 verified users who had new or worsening symptoms).

Comment: Among the subjects who should have stopped use for new or worsening symptoms, only 82.3% did. Subjects did not necessarily read or comply with labeling.

The applicant explored a number of secondary endpoints. Of interest from a safety standpoint was Secondary Endpoint 5 (SE5), which was the proportion of users who used a TDS for more than four days or used more than one TDS at a time. Post-mitigation, that proportion was 21% (152 of 727 verified users). This endpoint was largely driven by subjects who used the TDS longer than 4 days, which should not be a safety issue. Post-mitigation, a total of 22 verified users used more than one TDS at a time. Nonetheless, end-of-study interviews suggested that subjects who used more than one TDS at a time understood that only one TDS should be used. Forgetting to remove a TDS or trying more than one TDS to help with symptoms were some of the reasons offered by subjects for using more than one TDS at a time. These reasons would not be unique to the OTC setting.

Safety analyses were based on the entire user population (N=785). The median and mean exposures were 45 days. About 25% of users reported use for the full duration of the study (84 days). AEs were coded using MedDRA Version 11.0.

A total of 975 AEs were reported by 519 users. A total of 63.2% of the AEs were considered unrelated to Oxytrol. Overall, there was no apparent difference in the incidence of AEs or SAEs between younger (less than 65 year of age) and older cohorts.

There was one death due to viral pneumonia, determined to be unlikely to be related to Oxytrol use. There were 40 reports of SAEs by 35 users (4.5% of 785 users). For perspective, there were 8 reports of SAEs by 6 nonusers (8.6% of the 70 nonusers who provided data.) Only 1 of the user-reported SAEs was considered possibly related to the use of Oxytrol. This was a patient report of difficulty awakening from anesthesia that resulted in a transfer from a clinic to a hospital. A total of 152 users stopped using Oxytrol because of adverse effects. Table 2 shows the most commonly reported AEs.

Table 2. Frequently Reported AEs* by Age

	All Users N=785		Age <65 Years N=529		Age 65-74 Years N=129		Age ≥ 75 Years N=127	
	N	%	N	%	N	%	N	%
Application site irritation	142	18.1%	112	21.2%	19	14.7%	11	8.7%
Urinary tract infection	50	6.4%	27	5.1%	9	7%	14	11%
Dry mouth	32	4.1%	23	4.3%	4	3.1%	5	3.9%
Urge incontinence	24	3.1%	14	2.6%	5	3.9%	5	3.9%
Constipation	20	2.5%	17	3.2%	2	1.6%	1	0.8%
Back pain	18	2.3%	10	1.9%	5	3.9%	3	2.4%
Cystitis	16	2%	7	1.3%	5	3.9%	4	3.1%
Dysuria	12	1.5%	4	0.8%	3	2.3%	5	3.9%

Source: Adapted from Applicant's submission; Module 5.3 5 1, Section 12.4.5, Table 78, p. 173

*AEs that were considered possibly or probably related to Oxytrol therapy by investigators

The applicant and the primary reviewer provided a discussion of adverse events of special interest, including:

- UTIs
- Diabetes
- Bladder cancer
- Urinary retention
- Allergic reactions
- Skin irritation
- Anticholinergic effects
- Disorientation
- Narrow angle glaucoma
- Gastric retention
- Falls and accidents

UTIs: Lack of attention to the labeled warnings for UTI did not result in serious adverse events related to UTIs. Of the subjects who reported possible UTI symptoms at the enrollment interview and used the TDS (n=154), only eight were diagnosed with a UTI during the trial. Seven of the subjects recognized the symptoms and presented for care. The last subject was diagnosed at the EOS visit.

Sixty-one subjects reported UTIs during the trial; two were hospitalized for intravenous antibiotics; neither was diagnosed with sepsis or upper urinary tract complications.

Of 225 subjects who had at least one positive finding on EOS urinalysis, 20 were subsequently diagnosed with UTIs. The primary reviewer commented that most subjects who used the TDS despite having one or more symptoms of UTI had had OAB symptoms for more than one month. Acute UTIs are usually painful, and would not likely be tolerated for months without seeking treatment. The primary reviewer concluded “from the results of this trial, it appears that most consumers are unlikely to confuse UTI and idiopathic OAB, nor does it appear that diagnosis of UTI is likely to be delayed.”

Diabetes: Lack of attention to labeled warnings for diabetes did not result in serious adverse events related to diabetes. A total of 321 subjects who had labeled diabetes risk factors used Oxytrol, and most (75.4%) did not speak with their doctors before use. One subject was diagnosed with diabetes during the trial. She was a 41-year-old woman who was diagnosed two weeks after starting Oxytrol. She reported having OAB symptoms for five years. At enrollment she reported excessive thirst, hunger, and tiredness. She briefly re-started Oxytrol after the diagnosis of diabetes, but did not continue, citing cost as her reason.

Comment: This subject appears to have had both OAB and diabetes. If any of her OAB symptoms were related to her diabetes, a two-week delay after five years of symptoms is not clinically significant.

Bladder cancer: A total of 100 subjects with symptoms that could overlap with bladder cancer symptoms chose to purchase Oxytrol. No cases of bladder cancer were diagnosed during the trial, and no cases of bladder cancer were diagnosed among the subjects excluded from the use phase of the trial for hematuria, the most common presenting symptom of bladder cancer.

Urinary retention: Lack of attention to this labeled ineligibility did not result in acute urinary retention. There were no confirmed urologic diagnoses of acute urinary retention reported during the trial. This was, however, a commonly ignored labeling ineligibility at enrollment: 522 of 785 users reported a feeling of not being able to completely empty their bladders, and only three spoke to their doctors before use.

Allergic reactions: The primary clinical reviewer evaluated the reports with preferred terms that could indicate allergy, and concluded that “there did not appear to be any true allergic reactions.”

Skin irritation: Local skin reactions were commonly reported (186 reports by 177 users). One was serious: the subject had not used the TDS for two months prior to the diagnosis of a significant blistering where she had previously applied the TDS. She received wound care and intravenous antibiotics.

Comment: Skin reactions should be generally easy to self-diagnosis and easy to address by removing the TDS. There will be occasional individuals who may have serious reactions. This risk should be no different whether the product is OTC or Rx; a healthcare provider would not likely be able to predict who will have a serious skin reaction.

Anticholinergic effects: A total of 89 users reported 105 AEs that could be anticholinergic effects. None were serious. The most frequently reported were dry mouth (n=32), constipation (n=20, and dizziness/somnolence (n=29). Twenty-five subjects stopped using the TDS because of these effects.

Comment: The primary clinical reviewer notes that dry mouth and constipation are not on the proposed labeling but should be listed. I agree. These effects are important enough to users of the TDS to cause some of them to discontinue use.

Disorientation: This assessment overlapped with the anticholinergic assessment. The most frequently reported terms in this general class were dizziness/somnolence (n=29) and depression (n=5). There were two SAEs (schizoaffective disorder and convulsive syncope), which occurred in subjects with positive histories and were assessed as unlikely related to Oxytrol use. One subject (difficulty chewing) in this group permanently discontinued use of the drug.

Narrow angle glaucoma: All four subjects with narrow angle glaucoma wished to purchase the product but were excluded from the trial. There were no reports of glaucoma during the trial. Other OTC anticholinergic and adrenergic products have glaucoma warnings.

Gastric retention: Twenty subjects who reported gastric retention purchased and used Oxytrol. There were no reports of worsening gastric retention.

Falls and accidents: Seventeen subjects reported 19 AEs. Three permanently discontinued use of the TDS. There were seven SAEs involving falls and accidents reported, but only three SAEs in subjects who were using the drug at the time of their SAE.

Comment: Falls and accidents are common, and it is difficult to assess the contribution of the TDS to the SAEs in an uncontrolled trial. However, the fact that four of seven SAEs occurred in subjects who were not currently using the TDS provides a reassuring perspective.

8.3 Postmarketing Safety

The analysis of postmarketing safety did not identify new signals.

The applicant reviewed spontaneous reports for Oxytrol from the following databases:

- FDA's Adverse Event Reporting System (AERS) from 1-Jan-2003 through 31-Dec-2010
- World Health Organization (WHO) Vigibase for ex-US AEs from 1-Jan-2003 through 31-Aug-2010
- The American Association of Poison Control Centers (AAPCC) database from 1-Feb-2003 through 31-Aug-2011
- A summary of periodic adverse experience reports (PADERS) previously submitted to the FDA
- A summary of periodic safety update reports (PSURS) previously submitted to the European regulatory authorities

There is substantial overlap among these databases; they paint similar pictures of the postmarketing safety of the oxybutynin TDS.

IMS data estimate sales of over (b) (4) oxybutynin TDSs in the United States and (b) (4) in foreign countries for over 400,000 patient-years of treatment.

The adverse event profile in AERS and WHO is largely consistent with the findings of the clinical trials. Lack of effect, various application site reactions, and undesirable

anticholinergic effects predominate. Relative to sales, there are few AEs reported; however, reporting is voluntary and the number of reports is likely a small fraction of the number of AEs.

For the AERS analysis, the applicant chose to summarize only those events where Oxytrol was listed by the reporter as a suspect drug. By limiting the events to those in which the reporter listed Oxytrol as “suspect,” a minority of reports involving Oxytrol are captured. (However, the applicant also provided summaries of the Periodic Adverse Experience Reports (PADERS) previously submitted to the FDA, and the PADERS include all reports to the company that mention Oxytrol use.) There were 590 reports where Oxytrol was listed as the suspect drug in the AERS analysis. Individual AEs reported 6 or more times, in descending order of frequency, included

- Drug ineffective (N=14)
- Product quality issue (N=12)
- Application site erythema (N=11)
- Fall, confusion state (N=10 each)
- Condition aggravated (N=9)
- Application site pruritus, dizziness, headache, nausea (N=8)
- Agitation, application site dermatitis, constipation, dyspnea, urinary tract infection, vision blurred (N=6 each)

In the WHO Vigibase, 256 ex-US events were reported. Individual reports reported 5 or more times included:

- Drug ineffective (N=33)
- Application site reaction (N=12)
- Rash (N=8)
- Nausea (N=6)
- Application site erythema, dizziness, pruritus (N=5)

In the AAPCC database, there were 26 cases involving Oxytrol, 24 cases involving Gelnique (oxybutynin transdermal gel) and 12 cases involving oxybutynin transdermal gel, not otherwise specified. According to the primary clinical reviewer, most outcomes were “of minimal to moderate effects. Those with moderate to major effects were not further described. There were no new safety signals identified.”

The clinical review of the PSURs/PADERS and AERS reports identified no new signals. Overall, the pattern of AEs was expected based on labeling.

The primary clinical reviewer provided a focused assessment of postmarketing data for issues of special interest:

- Diabetes – There were 5 cases identifying “diabetes” in postmarketing safety databases for Oxytrol, Gelnique, or oral forms of oxybutynin. The applicant found no published reports in the past 15 years indicating delayed diagnosis of diabetes following presentation with OAB symptoms. The primary clinical reviewer concluded that “consumers with OAB symptoms appear unlikely to have a diagnosis of diabetes delayed to any significant extent due to the availability of Oxytrol for Women in the OTC marketplace.”

- Bladder cancer – There was one case of bladder cancer coincident with use of Oxytrol in AERS.
- UTI – In the PADERs and PSURs, there were 13 UTIs coded as SAEs.
- Pregnancy – no pattern of birth defects emerged from analysis of the pregnancy exposures in the postmarketing reports.
- Acute urinary retention – The applicant’s summary of the literature concluded that acute urinary retention in women is rare (7 per 100,000 women per year). An extensive literature evaluation identified a single case of urinary retention in a nursing home resident who was given oral oxybutynin. The case resolved spontaneously without treatment. There have been few cases of urinary retention reported in postmarketing databases. For example, there have been 6 events of urinary retention reported in association with Oxytrol use in AERS since 2003 launch. The primary clinical reviewer concluded that, “relative to the extensive drug distribution worldwide, spontaneous postmarketing reports of urinary retention are few.” The applicant states that “serious AEs when reported do not appear to have indicated Oxytrol as a causative agent.”
- Narrow angle glaucoma – The published literature includes a single report of an 80-year-old woman with acute angle closure thought to be caused by *oral* oxybutynin use in the Rx setting. According to the clinical review, “postmarketing experience does not identify a safety signal.”
- Falls, confusion, disorientation – FDA undertook a safety assessment of antimuscarinics, including Oxytrol, in 2010. The safety assessment evaluated cases of disturbance in consciousness. The Oxytrol NDA holder found 25 serious cases in which Oxytrol was used. As a result of the review, somnolence was added to the prescription label under a new CNS warning and patients were advised not to drive or operate machinery until the effects of Oxytrol were known (Oct 2012). This change was new class labeling. The clinical reviewer found two articles of interest related to oxybutynin and cognitive impairment^{4,5}; however, both articles addressed oral formulations, rather than the TDS. Per the primary reviewer, “there were a few reports in the postmarketing databases, but none that indicate a new safety signal.”

Comment: The proposed OTC labeling is not consistent with the updated Rx labeling regarding CNS warnings. Updated language is proposed in the Appendix.

8.4 Safety in the MATRIX Study

The MATRIX study (Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin) was conducted by Watson Labs in 2004-2005. It was an open-label, uncontrolled, observational study that followed Oxytrol users for six months of treatment *in the community prescription setting*. The stated goal of the study was to explore health-related quality-of-life changes. Safety findings were generally consistent with the data from clinical trials and with postmarketing databases.

⁴ Wagg A, Verdejo C, Molander U. Review of cognitive impairment with antimuscarinic agents in elderly patients with overactive bladder. *Int J Clin Pract.* 2010 Aug;64(9):1279-1286

⁵ Katz I Sands L, et al. 1998 Identification of medications that cause cognitive impairment in older people : the case of oxybutynin chloride *J am Geriatr Soc.* 1998; 4 :8-13

A total of 2881 subjects were enrolled after diagnosis of OAB by their physicians. Most (87%) of enrollees were female, the median age was 63 years, and half of subjects completed six months of therapy.

A total of 2834 AEs were reported by 1328 (46%) subjects. There were three deaths, two from cardiovascular causes and one from “natural causes,” all assessed by their prescribing physicians as unrelated to Oxytrol use. There were 168 subjects reporting SAEs, one of which (a UTI) was physician-assessed as drug-related. Some of the more common preferred terms for SAEs included: pneumonia (n=8), UTI (n=5), cerebrovascular accident (n=7), dizziness (n=5), and myocardial infarction (n=7). A total of 646 subjects reported an adverse event as their reason for discontinuing the study. Skin reactions were the most frequently reported AEs (n=1129). Dry mouth (n=64) was the most common anticholinergic effect. Other anticholinergic effects included constipation (n=58), dizziness (n=56), and blurred vision (n=36).

Regarding topics of interest from an OTC perspective:

Urinary tract infection was reported 82 times by 67 subjects. There were 10 subjects who reported urinary retention; all events were considered nonserious and drug-related except for one case. There was a single serious case of chronic urinary retention in an 86-year old woman that was not considered drug related. The diagnosis was made by ultrasound after at least 5 months of Oxytrol therapy. There were no new diagnoses of diabetes. There was a single diagnosis of prostate cancer after nearly five months of Oxytrol treatment. No bladder cancer was detected.

Comment: UTIs were fairly common despite physician management. Also, despite physician management, the single case of genitourinary cancer (cancer of the prostate) was made after more than five months of Oxytrol therapy. The percentage of subjects reporting SAEs was similar in the MATRIX trial, which took place in a prescription setting, compared with the CONTROL trial, which took place in an OTC setting (5.8% and 4.5%, respectively).

9. Advisory Committee Meeting

A meeting of the Nonprescription Drugs Advisory Committee (NDAC) was held on Nov 9, 2012 to discuss the application. In a close 6-5 vote, members voted no to the question: Does the totality of the data support that consumers can appropriately self-select to use the oxybutynin transdermal system?

Two of the six “no” votes hinged on two issues that could be addressed by labeling. One concern was the potential for central nervous system effects in the elderly who may already have some cognitive difficulties and may also be on drugs that potentiate the CNS effects of oxybutynin. Both members favored a maximum age limit for the OTC product to address the CNS issue. The second concern was the lack of information on the OTC label about behavioral techniques for managing OAB.

Another concern expressed by the committee was the possibility of missing a bladder cancer or bladder carcinoma in situ because a urinalysis will not precede TDS use in the OTC setting.

Concerns about cognitive effects in the elderly could be handled in labeling by setting an “ask a doctor” age limit for people over the age of 64. The language on CNS effects needs to be made consistent with recent changes in Rx labeling. I also recommend elevating the CNS language to the warnings section of the OTC label.

An age restriction would also speak in part to concerns about bladder cancer, as the average age at the time of diagnosis of bladder cancer is 73 (according to the American Cancer Society⁶ (ACS)). Annual preventative visits are covered by Medicare for all Americans over the age of 65. It is conceivable that the marketing around OTC TDSs, dissatisfaction with the OTC TDS, or the addition of the OTC TDS to the list of medications provided to one’s doctor at a check-up visit might prompt an increase in screening. Limiting the product to women also reduces the risk of undiagnosed bladder cancer as men are three times more likely than women to have bladder cancer.⁶

A consumer information leaflet (CIL) would help address remaining concerns, and possibly stimulate help-seeking behavior. A consumer leaflet could provide information about

- behavioral techniques
- the potential for drug-drug interactions in consumer-friendly language
- why it is important for men not to use
- why it is important to follow-up with a doctor if symptoms don’t improve

I do not believe that a description of behavioral techniques is needed on the Drug Facts label because understanding behavioral techniques is not a requirement for safe and effective use of the TDS; however, I recommend including summary information on behavioral techniques in a consumer leaflet. Behavioral techniques include limiting intake of fluids, caffeine, and alcohol; weight loss if overweight; and a variety of bladder control strategies. Behavioral techniques are recommended by professional groups as the American Urological Society (AUA) and the American College of Obstetricians and Gynecologists (ACOG). The following observations support adding information about behavioral techniques to a CIL rather than the Drug Facts labeling:

- Prescription labeling does not indicate that oxybutynin TDS is second-line or adjuvant therapy to behavioral therapy
- the AUA recommends trying behavioral techniques either before or concurrent with antimuscarinic therapies⁷
- ACOG is silent on the order in which therapies should be tried⁸
- Including high level information on behavioral techniques in an insert may stimulate OAB sufferers to seek help for their condition, particularly if the TDS does not satisfy their needs.

⁶ <http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics>

⁷ AUA Guideline: Diagnosis and treatment of overactive bladder (non-neurogenic) in adults. May 2012

⁸ ACOG Practice Bulletin: Urinary incontinence in women. June 2005, reaffirmed in 2011

Other committee concerns, use by men, use by pregnant women, and delay of diagnosis of diabetes are addressed elsewhere in this review.

10. Pediatrics

Proposed labeling states “Do not use if you are under the age of 18.” Prescription labeling says the safety and efficacy in pediatric patients have not been established. Given the indication and the lack of data in pediatric patients, the proposed labeling is acceptable.

The application does not trigger the Pediatric Research Equity Act because the applicant is not proposing a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

The application contains a letter from Watson Pharmaceuticals authorizing FDA to refer to Watson’s NDA 21-351 for oxybutynin transdermal system in connection with review of the current NDA. The regulatory team has determined that the application is a 505(b)(1) application.

The applicant did not use the services of any person debarred under the F, D, & C Act in connection with the application. The applicant has also submitted a signed and dated financial certification form certifying lack of financial conflicts. The application contains patent information and a request for exclusivity supported by the actual use study performed following FDA advice that the study was needed for the proposed OTC product. The patent and exclusivity information will undergo a regulatory review.

FDA inspectors inspected four clinical sites of the Actual Use Study (CONTROL); all sites were satisfactory. Dr. Gershon from FDA’s Office of Scientific Investigations (OSI) reviewed the reports of the inspections. The sites and her assessments are as follows:

1. Site #10, Stevenson Family Pharmacy in St. Joseph, MO (n=56), no action indicated (NAI).
2. Site #12, Matt’s Medicine Store in Independence, MO (n=52), deviation from regulations (VAI). The deviations were around performance of an end-of-study urinalysis and failure to re-consent subjects after an amendment to the protocol added an end-of-study urinalysis. OSI did not believe that the deviations were significant in terms of subject safety. I concur, and do not believe the deviations affected the integrity of the study results.
3. Site #24 in Baltimore, MD (n= 26), NAI.
4. (b) (4) (The Contract Research Organization with the source data and trial master file), NAI.

12. Labeling

The applicant provided five label comprehension studies (LCSs) and three self-selection studies (SSSs), all reviewed by the FDA Social Scientist, Barbara Cohen. Drug Facts and other carton labeling were evaluated by the entire team and reviewed in detail by the FDA interdisciplinary scientist, Maria Ysern, and by James Schlick from DMEPA. I have borrowed from these more detailed reviews to write the summary below.

12.1 Label Comprehension Studies and Self-Selection Studies

Designing, testing, and re-designing the label was an iterative process involving five LCSs and three SSSs. The Social Science review focused on the pivotal LCS as the most recent and rigorous study that used a label similar to the label proposed for marketing. Earlier studies were evaluated to fill in the gaps from the pivotal study or to complement the findings of the pivotal study.

LCSs and SSSs included:

- Pivotal LCS– conducted in late 2010.
- LCS in subjects over 65 years of age with self-reported overactive bladder (OAB) symptoms – conducted in early 2010.
- LCS of diabetic warnings among general OAB sufferers – conducted in early 2010.
- LCS of enhanced pregnancy warning among women of childbearing age – conducted in early 2010.
- LCS among NL (normal literacy) female OAB sufferers, LL (low literacy) female OAB sufferers, general population female non-sufferers, and men – conducted in 2008.
- SSS in pregnant women with OAB symptoms – conducted in late 2010.
- SSS in men with OAB symptoms – conducted in late 2009.
- SSS in women with OAB symptoms; also four other subpopulations: men, diabetics, those with glaucoma, and those pregnant or nursing – conducted in early 2009.

12.1.1 Evaluation of the Pivotal Label Comprehension Study (Study 10053)

The pivotal LCS was a multicenter study involving three cohorts:

- Cohort 1 – females 18 years+ with self-reported OAB, general population, n=472
- Cohort 2 – females 18 years+ with self-reported OAB, low literacy augmentation, n=120
- Cohort 3 – females 44 years+ with self-reported risk of diabetes symptoms, n=160

Cohorts 1 and 2 were asked identical questions covering OAB self-identification and a variety of medical issues related to labeled warnings. Cohort 3 was asked questions to assess the comprehension of labeling related to diabetes risk. Subjects were provided a mock-up package and allowed to read the labeling at their own pace. They were then interviewed using a questionnaire consisting of open-ended, mostly scenario-based questions. The applicant determined objectives of higher medical consequence and set target success thresholds for the lower bound of the 95% confidence interval at 90%; target success thresholds for objectives of lower medical consequence were set at 85%.

Table 3 and Table 4 summarize findings for Cohorts 1 and 2. For the objectives with a 90% threshold, allergy warnings scored well regardless of literacy. Narrow angle glaucoma scored least well and did not meet the threshold for either group; however, the population tested was a general one, and it seems reasonable that sufferers of glaucoma may be more attuned to reading labels. Glaucoma warnings appear on other OTC products that have anticholinergic or adrenergic effects. LLs did not do well on understanding the idea that symptoms should be present for 3 or more months (88% NL versus 71% LL). The Social Science reviewer notes that emphasizing the 3-month duration by formatting changes may be helpful; I concur. Both this study and the actual use study showed some confusion around the gastric retention and urinary retention warnings; to hone in on medically important gastric and urinary retention, the applicant has revised proposed labeling to clarify that a doctor should have diagnosed these conditions.

Comment: Clarifying that a doctor should have diagnosed the condition should limit the number of people for whom the “do not use if” language applies to those who have a good medical reason to not use the product.

Cohort 3, women at risk for diabetes, scored in the 80-85% range on diabetes warnings. Only two diabetes warnings were tested: family history and excessive thirst. Extreme hunger and increased tiredness were not assessed. Comprehension of ask a doctor if there is a family history of diabetes scored at 83% (LB). Comprehension of ask a doctor if there is excessive thirst scored at 82% (LB).

Comment: Optimally, extreme hunger and increased tiredness should have been tested as new elements on OTC labeling. However, from a clinical perspective, I find it acceptable that there was a reasonable understanding of the tested diabetes language as it is unlikely that the TDS would have any effect on the osmotic diuresis that underlies the urinary symptoms of diabetes. Unsuccessful TDS use by women who have diabetes rather than OAB may actually prompt them to seek medical care sooner, rather than later, for their urinary symptoms, which in turn may lead to an earlier diagnosis of diabetes.

The Social Science review evaluated methodological issues of the study and concluded that the findings could be somewhat upwardly biased because of low numbers of LL subjects in Cohort 1 (6%) and Cohort 3 (10%). Additionally, the augmented LL Cohort 2 was recruited from only two sites, suggesting that Cohort 2 may not be representative of the U.S. population of LLs. In addition, the diabetes risk calculator that was administered before the diabetes questionnaire in Cohort 3 may have cued subjects to the topic of interest.

The statistical reviewer assessed the endpoints for the pivotal label comprehension study and did not identify any statistical issues to preclude approval.

The general conclusions from this study were that allergy warnings did well; other warnings were in the 80-90% range among the general population. There was some potential for upward methodological bias in the study. On subgroup analysis, older respondents for the most part did not have significantly less comprehension than younger respondents.

Table 3. Pivotal LCS 10053 – Results for Cohorts 1 and 2 – Objectives of Higher Medical Consequence

Objectives of Higher Medical Consequence (success threshold at 90%)	% Correct Cohort 1 Point Estimate (Lower bound of CI)	% Correct Cohort 2 Point Estimate (Lower bound of CI)	Normal Literate Point Estimate	Low Literate Point Estimate
1. Have urinary retention (are not able to empty your bladder)	91.3 (88.4)	84.2 (76.4)	92.7	81.6
2. Have been told by a doctor that you have gastric retention (your stomach empties slowly after a meal)	89.8 (86.7)	74.2 (65.4)	90.9	74.3
3. Narrow-angle glaucoma	87.7 (84.4)	80.0 (71.7)	90.2	74.3
4. If allergic to oxybutynin	95.1 (92.8)	91.7 (85.2)	95.9	90.1
5. You have an allergic reaction to this product	93.2 (90.6)	90.8 (84.2)	93.0	92.1
6. You have severe redness, itchiness or blistering at the site of application	88.6 (85.3)	89.2 (82.2)	88.9	88.2

Source: adapted from Appendix 1, FDA Social Science Review

Table 4. Pivotal LCS 10053 – Results for Cohorts 1 and 2 – Objectives of Lower Medical Consequence

Objectives of Lower Medical Consequence (success threshold at 85%)	% Correct in Cohort 1 Point Estimate (Lower bound of CI)	% Correct in Cohort 2 Point Estimate (Lower bound of CI)	Normal Literate Point Estimate	Low Literate Point Estimate
7. Symptoms for at least 3 months	87.3 (83.9)	69.2 (60.1)	88.0	71.1
8. Will not work for stress incontinence	77.3 (73.3)	63.3 (54.1)	79.5	59.9
9. A history of kidney stones	89.8 (86.7)	90.8 (84.2)	90.5	88.8
11. Liver disease	83.9 (80.3)	90.0 (83.2)	84.5	86.8

Source: adapted from Appendix 1, FDA Social Science Review

12.1.2 Evaluation of the Earlier LCSs and Three SSS

LCS #92101 evaluated label comprehension among female OAB sufferers who were 65 and older. It was a multicenter study that recruited 350 subjects, 12% of whom were LL. There was overlap between the objectives of this study and the pivotal study, but this study also assessed comprehension of the symptoms of urinary tract infections (UTIs), directions for use, and the ‘stop use and ask a doctor’ conditions. Performance on the overlapping objectives was similar to performance in the pivotal LCS. Overall comprehension of UTI symptoms was high, ranging from 89% to 94% (LB of 95% CI). Understanding of wearing one TDS at a time and wearing the first and second TDSs for 4 days was high (98% LB, 96% LB, and 97% LB, respectively.) Results for the ‘stop use and ask a doctor’ conditions ranged from 85% LB for allergy to 96% LB for symptoms getting worse.

LCS #92099 evaluated comprehension of diabetic warnings among OAB sufferers. This multicenter study recruited 360 subjects to Cohort 1 (general population) and 230 subjects to Cohort 2 (LL). As with the pivotal study, family history of diabetes and excessive thirst were the two tested objectives. Unlike the pivotal study, the study provided a reasonably robust sample of LL consumers. The overall scores were somewhat higher than the scores in the pivotal study, but LL consumers had lower scores than the general population in either study. Understanding of family history scored at 90% LB; point estimates were 93% NL versus 79% LL. Understanding the excessive thirst warning scored at 92% LB; point estimates were 95% NL versus 71% LL.

LCS #92062 evaluated comprehension of an enhanced pregnancy warning (understanding that a doctor should be consulted if pregnancy is a possible cause of OAB symptoms) among women of childbearing age. It was a multicenter study that recruited 350 subjects to Cohort 1 (general population) and 224 subjects to Cohort 2 (LL). The scenario described a woman with urinary frequency who had missed two periods. Three questions unrelated to pregnancy were asked to decrease bias. Understanding of the pregnancy question in the general population scored at 90% LB; point estimates were 92.9% NL versus 83.3% LL. Of note, a scenario describing a subject who only had OAB symptoms for two weeks did not score particularly well; only 26% (point estimate) said it was not okay to use the TDS. The sponsor ascribed the results to confusion about the scenario (symptoms and duration) and tested a simpler question (duration only) in the pivotal LCS.

LCS #82023 was an earlier (2009) multicenter study that evaluated comprehension of numerous labeling elements among four cohorts:

- Cohort 1, NL females with OAB, n=196
- Cohort 2, LL females with OAB, n=204
- Cohort 3, general population of females without OAB, n=199
- Cohort 4, general population of men, n=76

The study tested 33 communication objectives in each of the first 3 cohorts and, in Cohort 4, tested whether men understood the product was not for them. Men generally understood that the product was not for them (86% LB, 95% point estimate). Other results were not notably different from the findings of the later LCSs.

SSS #10054 was a multicenter study to evaluate appropriate self-selection in pregnant women with OAB symptoms. The study recruited 308 women into Cohort 1 (general population) and 127 women into Cohort 2 (LL). The study tested whether women understood that urinary frequency could be an early sign of pregnancy, and that they should ask a health professional before use if pregnant or nursing. Women were asked if the product was okay for them to use right now. Unmitigated results showed that Cohort 1 had an 84.2% LB and a point estimate of 88.3% correct response. The low literacy cohort had LB of 54% with a point estimate of 63% correct response. The Social Science reviewer took issue with the mitigation process as it involved a challenge question that appeared to coax for the correct response. Mitigation modestly improved the results. The applicant made an adjustment to the female icon on the proposed labeling following this study. The proposed label shows a slender silhouette of a woman with a narrow waist, as opposed to the stylized tent-like dress used on the labeling in this study. I agree with the Social Science reviewer who stated that “given that visual icons may help with comprehension, particularly among the less literate, I think that this is a significant improvement.”

SSS #92061 was a multicenter study among men with OAB symptoms to evaluate the ‘do not use if you are male’ warning. As in the proposed packaging, the packaging in this study was pink and had a prominent female silhouette leaning on the “O” in “Oxytrol for Women.” The study recruited 354 men into Cohort 1 (general population) and 217 men into Cohort 2 (LL). After mitigation, 92% (point estimate; LB 88.1) of the general population of men made a correct decision. The LL cohort had almost identical scores.

SSS #2008-19 was the earliest SSS conducted (early 2009). It was a multicenter study evaluating self-selection in women with OAB symptoms (NL (n=218) and LL (n=137), men (n=172), diabetics (n=42), subjects with glaucoma (n=12), and subjects who were pregnant or nursing (n=10). The study used an earlier version of labeling and suffered some methodological flaws, including the possibility of inclusion of professional respondents, as discussed in the Social Science review. This was, however, the only study in which those subjects who agreed to undergo a pelvic exam and lab testing had their self-selection checked against a physician’s diagnosis. Overall, 89.4% (NL)-91.2% (LL) of subjects agreeing to a physical exam correctly self-diagnosed the condition. No subject reported gross hematuria; there were five subjects who had microscopic hematuria and the physician stated that the subject should not select the product based on the hematuria and other findings. Four of the five had concurrent OAB. Ages were 31, 43, 48, 65, and 74 years old. Information on ultimate diagnosis was not provided and does not appear to have been obtained.

12.1.3 Conclusions and Recommendations Based on Findings of LCSs and SSSs

Regarding consumer self-identification of OAB, the Social Science reviewer recommends emphasizing the “at least” phrase in the labeling: “You may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months.” I agree. People did not do well on the duration of symptoms when they were asked a scenario combining symptoms and duration; they did better when cued to look for duration only.

However, in a real consumer setting, people will have to sift through their own complicated scenarios. To help with understanding that OAB is a chronic condition (and to differentiate it from more acute conditions, such as UTI), it seems reasonable to emphasize “at least” or “at least 3 months.”

Regarding diabetes, the Social Science reviewer recommends that the risk factor, positive family history, be put in a bullet separate from, but contiguous to, a bullet for the symptoms of diabetes. She points out that positive family history was better understood than the only symptom tested in LCS (excessive thirst), with the result that it might get readers to focus on diabetes symptoms more than if it wasn't present at all. On the other hand, Advisory Committee (AC) members questioned whether family history was necessary on labeling, as a positive family history is only one (and not the most predictive) of many risk factors for diabetes. By itself, a positive family history would not likely result in a screening test for diabetes for a woman who presents to her doctor with the symptoms of OAB. I agree with the AC that asking a doctor if one has a family history of diabetes is unnecessary and recommend deleting the family history of diabetes from labeling.

Comment: As noted earlier, I do not think that misunderstanding of the symptoms or risk factors for diabetes will have significant clinical consequence. It is unlikely that the diagnosis of diabetes would be delayed in consumers using the TDS because it is unlikely that the TDS would have any effect on the osmotic diuresis that underlies the urinary symptoms of diabetes. Unsuccessful TDS use by women who have diabetes may even prompt them to seek medical care sooner, rather than later, for their urinary symptoms, which in turn may lead to an earlier diagnosis of diabetes.

Regarding pregnancy, the SSS did not meet its threshold. The LL cohort underperformed the NL cohort by about 25%, which is more than the spread seen for other labeling elements. The proposed labeling has replaced the female silhouette wearing a tent-like dress with a female silhouette with a slender waist. As noted in the Social Science review, “Given that visual icons may help with comprehension, particularly among the less literate, I think that this is a significant improvement.” I concur. Additionally, oxybutynin is Pregnancy Category B, which means animal data are negative for pregnancy risk but human data are lacking. Pregnancy Category B drugs are accepted in the OTC marketplace. As an obstetrician I have found that most women obtain prenatal care once they know they are pregnant, and basic care includes counseling about medication use. For these reasons, I find the pregnancy labeling adequate.

Regarding men, 90% (point estimate) understood that the product was not for them. It is unlikely that men's understanding that the product is not for them can be improved by more labeling enhancements; the label is pink, ‘Oxytrol for Women’ is prominently displayed, and a clearly female silhouette is also prominent. The concern with men is that prostate disease may present with symptoms mimicking OAB, and a man with prostate disease who uses an anticholinergic drug risks acute urinary retention. However, it seems unlikely that a drug that causes an average increase in urinary volume of about 1 tablespoon of urine would precipitate many cases of acute urinary retention. If a man did use Oxytrol for Women and suffered acute urinary retention, the ensuing visit to the ER for this painful but not life-threatening condition might actually hasten the diagnosis of prostate disease. The prescription product, Oxytrol, which is approved for men and women, is identical to the proposed OTC product; therefore a man using the OTC product would not be exposing himself to the wrong dose or dosing

regimen for his OAB. For these reasons, I find it acceptable that about 10% of men did not understand the “for Women” message.

The Social Scientist notes that one AC member raised a concern about parents medicating young children; she noted in her review that comprehension of age limitations was high. The initial LCS had a question about whether it was okay to give an eight-year-old Oxytrol, and comprehension was very high, with lower bound of 95%, 96%, and 98% among NL female OAB sufferers, LL female OAB sufferers, and general female OAB non-sufferers, respectively.

12.2 DMEPA’s Labeling Review

FDA’s Division of Medication Errors and Prevention Analysis (DMEPA) found the proprietary name, “Oxytrol for Women,” acceptable. DMEPA had additional comments related to the product and labeling, most of which I recommend conveying to the applicant. There were two DMEPA comments, however, with which I disagree:

- 1) DMEPA recommends relocating the female graphic because it interferes with the proprietary name and may be misinterpreted as a ‘p.’ I disagree for several reasons. First, the female silhouette does not look like a ‘p’ to me. Second, a similarly-positioned female graphic was tested well in the pivotal label comprehension study; moving the graphic away from a position of prominence could interfere with the message that the product is for women. Finally, if a consumer confuses the silhouette of a female who has breasts, a narrow waist, a dress, high heels and bobbed hair for a ‘p,’ and the consumer thinks she is purchasing “poxytrol for Women,” it is unclear what safety problem would ensue.
- 2) DMEPA would like the name of the product that is inked onto the TDS to be more visible if the product falls to the floor, and would like the company to commit to this change within one year of approval. The DMEPA reviewer posits that a more visible color would make it more likely that someone would see the TDS on the floor and remove it before a young child retrieves and misuses it. There are no reported safety events for Oxytrol driving the recommendation. Making the ink more visible to an adult may also make it more visible to a young child. The visibility of the ink on a floor may depend on the color of the floor as well as the color of the ink. Similarly, the visibility of the ink on a person’s skin would depend on the color of the skin. At this time there appears to be no compelling reason to require the company to commit to a manufacturing change. If a safety issue related to the ink is identified in the future, we would be in a stronger position to require a change. However, DMEPA has conveyed the concern to the applicant; a response is pending.

12.3 DNRD’s Labeling Review

The DNRD labeling review focused on regulatory compliance rather than clinical content. I concur with their recommendations.

12.4 Additional Labeling Comments

My clinical recommendations appear in track changes in the Appendix and are generally aligned with the recommendations in the primary clinical review. The main points are:

- Provision of a consumer leaflet to provide basic information about behavioral techniques, and to encourage help-seeking behavior for consumers who would benefit from a visit with their healthcare provider
- An “ask a doctor” age restriction for people over 64
- Removal of “ask a doctor before use if you have a history of diabetes in your immediate family
- Strengthening of the CNS warning language to be consistent with the language on Rx labeling
- Addition of dry mouth and constipation to the list of side effects

I differ with a few recommendations in primary clinical review:

- Adding ulcerative colitis, myasthenia gravis, gastroesophageal reflux disease, and esophagitis to the “ask a doctor before use” section. I disagree for several reasons. It may be difficult to find consumer friendly language to describe these conditions. Also, consumers with these conditions should be under doctor supervision, and the doctor should be aware of and supervising all drug use. In addition, we have antihistaminic, anticholinergic drugs (sleep aids and allergy therapies) on the OTC market that do not drill down to these disease conditions on labeling, and we have not detected postmarketing signals as a result. The general warnings about “your stomach empties slowly” and the CNS warnings may be adequate.
- Adding ask a doctor before use if you have cardiac disease. The clinical reviewer recommended this addition because there are cardiac warnings on foreign labeling. Because U.S. labeling does not include cardiac warnings, and we have not detected a signal in the years of postmarketing surveillance, I do not recommend adding this warning to the OTC label at this time.

I differ with one labeling recommendation in the CMC review. The CMC review recommends removing “patch” from all labeling and replacing it with the words “transdermal system” or the acronym TDS. CMC is trying to develop uniform nomenclature for transdermal products. (Of note, the dosage form/route listed in the Orange Book for prescription Oxytrol is “film, extended release; transdermal.”)

While I agree that the nonproprietary name on the PDP and Drug Facts labeling should be oxybutynin transdermal system (and it is), the remaining uses of the word “patch” seem acceptable to me. As the company has done an extensive consumer program to develop the labeling, and the tested labeling used the simple term “patch,” it may be confusing to move to the more complex text “transdermal system” or the acronym “TDS.” “Patch” appears about 10 times in the Directions section of labeling alone, and consumers did reasonably well with the directions in the actual use study. The word “patch” has been used in another OTC label (Salonpas). I am not aware of any consumer testing of “transdermal system” for OTC products. While I agree that uniformity in nomenclature is important, the time to convey this

recommendation is *before* consumer testing of labeling. Going forward with new products, it would be reasonable to request and test “transdermal system” or TDS.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend approval of the application contingent on

- Final agreement on labeling
- Satisfactory final inspection reports for the manufacturing and testing sites
- Satisfactory resolution of proposal for acceptance criteria for the presence of (b) (4)

13.2 Risk Benefit Assessment

FDA has already determined that the risk-benefit profile for the oxybutynin TDS is acceptable in a prescription setting. The issue for this application is to decide if the risk-benefit profile for oxybutynin TDS remains acceptable when the drug is used in the OTC setting.

Oxybutynin TDS has characteristics that make it a reasonable candidate for OTC marketing. Both the condition it treats and its adverse effects are symptomatic, which means that both the benefits and the adverse effects should be apparent to the consumer. Symptoms can be reasonably described on an OTC label.

The applicant followed an iterative path to developing OTC labeling. That path involved a series of label comprehension and self-selection studies. Along the way, the labeling benefited from the lessons learned from previous studies. Overall, consumers asked to focus on labeling in LCSs and SSSs showed acceptable comprehension of labeling text. The consumer studies culminated in an actual use study, which met its a priori endpoint and did not reveal any unexpected safety signals. The actual use study also showed that many consumers did not comply with labeled cautionary language. However, within the limitations of a 785-subject actual use study, significant safety issues related to TDS use were not detected, despite consumer inattention to labeling.

The clinical trial data and postmarketing experience support that the oxybutynin TDS has a relatively benign safety profile. Much of the warning language on Rx labeling covers anticholinergic class effects, rather than effects observed in trials of the oxybutynin TDS. The modest anticholinergic activity of the oxybutynin TDS makes it likely that the more serious events described by class labeling, such as acute urinary retention or gastric retention, will occur rarely. This appears to be borne out in the postmarketing reports.

Because both the benefit and the risks of the TDS are symptomatic, people who use the TDS can make a personal risk-benefit decision, and the data on drug use suggest that they do. (See

Section 7.) Like other anticholinergic drugs for OAB, the oxybutynin TDS has modest effectiveness. Most users do not remain on the TDS beyond a few months; however, a small subset of users continues using the TDS long-term. Whatever factors (inadequate effect? cost? side effects?) drive most users to discontinue using the TDS, these factors should be equally apparent in an OTC or Rx setting.

Except for local skin irritation, the adverse effects caused by the TDS are likely related to its anticholinergic effects. Some users will experience dry mouth, constipation, dizziness, blurry vision, or sleepiness.

One area of concern for the FDA during OTC development and expressed by the Advisory Committee was delay of diagnosis of conditions with symptoms that overlap those of OAB. OAB is a diagnosis of exclusion. As detailed in the reviews, the data and clinical experience do not support that there will be clinically important delays in the diagnosis of urinary tract infection, diabetes, or pregnancy if a consumer tries the Oxytrol TDS. Theoretically, there could be delays in diagnosis of the subset of bladder cancers that are first detected through urinalyses showing microscopic hematuria; however, it is also possible that these cancers will be picked up earlier for reasons detailed in Section 9 of this review. Additionally, adding a recommendation to the label that women over 64 ask a doctor before use may encourage women at highest risk for bladder cancer to consult a doctor about their symptoms.

Another area of concern for the Advisory Committee was the lack of information about behavioral therapies in the proposed label. For reasons detailed in Section 9, I believe this issue can be addressed in a consumer information leaflet.

There is one area of uncertainty that remains a concern for me, and that is the potential for central nervous system (CNS) effects. A recent FDA evaluation of sporadic postmarketing reports of CNS-related AEs for OAB drugs in this class resulted in upgraded warning language on Rx labeling (Oct 2012). While CNS effects are not commonly reported, they can result in serious events. Although the clinical trial data did not raise a signal about CNS effects, there are limitations to applying the data from clinical trials to the greater OTC population. CNS effects might be a special problem for consumers who use drugs that delay the metabolism of oxybutynin or that act at the same antimuscarinic receptors. Older adults are the largest group of vulnerable consumers: they may be on many drugs, have cognitive issues at baseline, and be at particular risk of serious complications from dizziness and other CNS effects because of osteoporosis, anticoagulation, or other medical factors.

It is true that drugs with anticholinergic CNS effects, such as drugs for allergy and sleep, are already widely available on the OTC market. It would therefore be difficult to deny OTC status to the oxybutynin TDS on these grounds alone. How the TDS compares with these other drugs is unknown because there are no comparative data. Limited data suggest that oral oxybutynin is associated with greater cognitive impairment than oral diphenhydramine; however, how or whether the findings apply to the TDS is unknown.⁹

⁹ Katz IR, Sands LP, et al. Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc.* 1998 Jan;46(1):8-13

Considering the potential for drug-drug interactions, the likelihood that the TDS will be used by many older adults, the seriousness of potential consequences of CNS effects, and the recent changes in the CNS warnings on the Rx label, I recommend that the CNS warnings be strengthened and elevated to the Warnings section of Drug Facts labeling.

13.4 Recommendation for Postmarketing Risk Evaluation and Management Strategies

Routine postmarketing pharmacovigilance

13.5 Recommendation for other Postmarketing Requirements and Commitments

None

13.6 Recommended Comments to Applicant

None

14. Appendix – Recommendations for Drug Facts Label

3 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLEYANNE FURLONG
12/05/2012