

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202211s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 21, 2012
From	Andrea Leonard-Segal, M.D.
Subject	Division Director Summary Review
NDA/BLA #	NDA 202-211
Supplement #	
Applicant Name	Merck Consumer Care, Inc.
Date of Submission	March 26, 2012
PDUFA Goal Date	January 26, 2013
Proprietary Name / Established (USAN) Name	Oxytrol for Women® / Oxybutynin
Dosage Forms / Strength	Transdermal System / 3.9 mg per day. The product is intended to remain on the skin for 4 days.
Proposed Indication(s)	Treats overactive bladder in women
Action/Recommended Action for NME:	Approval pending completion of satisfactory labeling negotiations

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
DNCE Medical Officer Review 11/19/2012	Ryan Raffaelli, M.D.
DRUP Medical Officer Review 02/17/12	Donald McNellis, M.D.
Statistical Review	Yunfan Deng, Ph.D. and Yan Wang Ph.D.
DNCE Pharmacology Toxicology Review	Xinguang (Cindy) Li, Ph.D. and Paul Brown, Ph.D.
CMC Review 11/16/2012/OBP Review Verbal and e-mail communications	Sheldon Markofsky Ph.D., Carol Strasinger, Ph.D., Terrance Ocheltree Ph.D/ Tapash Ghosh, Ph.D Eric Duffy, Ph.D.
CDTL Review 12/05/12	Lesley Furlong, M.D.
OSE/DMEPA Reviews 11/9/12 and 12/11/12	James Schlick, RPh, Todd Bridges, RPh, and Kellie Taylor, PharmD
OSE Pharmacovigilance Data Review	Carolyn Volpe
OSE Division of Epidemiology(DEPI) I and DEPI II Drug Use Review	Patty Greene, PharmD., Elizabeth Kang, MPH, Judy Staffa Ph.D., RPh, and Tarek Hammad M.D., Ph.D
Social Scientist Review	Barbara R. Cohen, MPA
Office of Scientific Investigations Clinical Inspections Summary	Sharon Gershon, PharmD
DNRD Labeling Review	Maria Ysern and Ruth Scroggs PharmD.

OND=Office of New Drugs

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

CDTL=Cross-Discipline Team Leader

DNCE=Division of Nonprescription Clinical Evaluation

DNRD=Division of Nonprescription Regulation Development

Signatory Authority Review Template

1. Introduction

Merck Consumer Care, Inc. submitted a new drug application to partially switch the prescription oxybutynin transdermal system (TDS) over-the-counter (OTC) for the treatment of overactive bladder (OAB). The prescription product is a topical “patch” that is approved for both men and women; however, because of clinical concerns about men with undiagnosed prostate disease who might be at risk for urinary retention in the OTC setting if they were to use the oxybutynin TDS, the proposed OTC population is adult women. There is no intrinsic reason why men with a diagnosis of OAB cannot use this product.

The Cross-Discipline Team Leader and discipline reviews cover the relevant points for this application. This review will focus on any areas of controversy or disagreement that I may have with the recommendations of the other reviewers and will emphasize areas that have been raised as possible clinical concerns regarding the approval of Oxytrol for Women®.

2. Background

A detailed review of the regulatory history of the Oxytrol for Women® development program can be found in Dr. Raffaelli’s clinical review.

Overactive bladder is a common, symptomatic, chronic condition in adults, and especially among older adults. The severity of the symptoms fluctuates in any given patient. Symptoms of OAB, as defined by the International Continence Society in 2002, include urinary urgency (a sudden compelling desire to urinate that is difficult to defer and the most prominent OAB feature) with or without urinary incontinence associated with frequency and nocturia in the absence of other local or metabolic factors that would account for the symptoms. There is no physical finding or abnormal laboratory test that establishes the diagnosis of OAB. The condition adversely impacts quality of life by interfering with sleep, and causing embarrassing social limitations such as the need to wear diapers and bathroom seeking behavior. Patients restrict fluids and avoid sexual intimacy because of the condition. There is an increased incidence of falls and fractures among older patients with OAB which may result from rushing to the bathroom to avoid urge incontinent episodes.¹

Urinary symptoms overlap and may co-exist with such conditions as diabetes, urinary tract infections (UTI), pregnancy, prostate disease, and stress incontinence. Treatment modalities for OAB in addition to medication include lifestyle changes and other types of behavioral therapy.

FDA has approved various prescription drugs for OAB including anticholinergic drugs like oxybutynin and the adrenergic agonist mirabegron. Oxybutynin chloride was approved in

1975. The active ingredient, oxybutynin, has been available in oral tablets for the overactive bladder indication since 1998 and is also available as a syrup formulation and a transdermal gel formulation. The oxybutynin TDS was approved in Feb 2003 under the brand name Oxytrol (NDA 21351) for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

The active ingredient is a tertiary amine ester which is a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. As such, it relaxes bladder smooth muscle, and increases both urinary bladder capacity and the volume to first detrusor contraction. The average daily dose of oxybutynin absorbed from the transdermal system, (which contains 36 mg of oxybutynin) is 3.9 mg and each TDS (patch) is worn on the skin for four days before replacing it with another. Oxybutynin is metabolized by the cytochrome P450 enzyme system (especially CYP3A4). Steady state is reached during the wearing of the second TDS. The half-life of oxybutynin after patch removal is 7 – 8 hours.

The prescription labeling states that no drug-drug interaction studies have been performed, but Dr. Raffaelli reviewed an article that reported a 2-fold increase in oxybutynin bioavailability when taken concomitantly with itraconazole, a strong CYP 3A4 inhibitor. Labeling has addressed the impact on metabolism via CYP3A4 of other OTC drugs such as cimetidine.

It is important to note that the antimuscarinic effect of oxybutynin is non-selective. Thus it can be associated with anticholinergic effects elsewhere in the body.

To support Oxytrol's development for OTC use, the applicant performed 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
- Consumer Trial of Oxytrol (CONTROL) Actual Use Study

Merck provided a summary of the safety data from clinical trials and postmarketing data derived from spontaneous reports, a summary of adverse events (AEs) reported in a phase 4 study called Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin TDS (MATRIX study) conducted by Watson Pharmaceuticals, the prescription NDA holder, and a targeted review of specific safety topics of interest. No new efficacy studies were performed or deemed necessary for the development of the OTC drug.

3. CMC/Device

All pending manufacturing site issues have now been addressed. Through verbal and e-mail communications with Dr. Eric Duffy (Director, Division of New Drug Quality Assessment III), I learned that the FDA District Office has updated a potentially unacceptable facility evaluation to a Voluntary Action Indicated which means that a facility, originally in question, is now found to be acceptable. The chemistry review addressing this issue is not yet archived.

The applicant has provided sufficient information to assure that the drug substance is deemed acceptable and that the identity, strength, and purity of the drug product are also acceptable.

(b) (4)
the CMC team has recommended a 2-year shelf life for this product.

When Dr. Furlong finalized her CDTL review there was a question as to the acceptance criteria that the chemists would require for the presence of (b) (4) in the product. Since then, they have decided to accept specifications for (b) (4) of (b) (4) for the Oxytrol TDS.

The CMC information for the proposed OTC product was very similar to that of the prescription product (NDA 21-351), so the submission cross-referenced or duplicated most of the CMC data from that application. The biopharmaceutics review evaluated only the proposed *in vitro* drug release method and acceptance criteria and the reviewer determined that the changes in the manufacturing equipment had no impact on the bioavailability of the drug product.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No new nonclinical studies were conducted for this NDA.

It should be noted that a lot of thought went into the determination that dermal carcinogenicity studies and chronic dermal toxicity studies in animals, which were not performed for the marketing approval of the prescription product, did not need to be conducted for the approval of the switch application. The thinking of the pharmacology reviewers that led to this determination was as follows:

- Neither oxybutynin, nor its main metabolite, are structurally similar to any compounds commonly associated with genotoxicity or carcinogenicity.
- All genotoxicity studies on oxybutynin were negative.
- Oral carcinogenicity studies were negative.
- The administration sites of the patch will be rotated among the abdomen, hips, and buttocks. Any potential risk of application site neoplasm would be further minimized by instructions in the product labeling to avoid re-application to the same site within a 7-day period.
- There has been no carcinogenicity signal in clinical studies on the oxybutynin patch or in postmarketing data despite the fact that oral oxybutynin products and transdermal oxybutynin have been used clinically for over 30 years and 10 years respectively.

The FDA Division of Pharmacovigilance (DPV) completed an FDA Adverse Event Reporting System (AERS) search for skin cancer associated with use of the oxybutynin TDS from the time of approval through June 2102 (over 9 years) and no skin cancers were identified. During this period of time, over 40 million units of the medication were distributed worldwide with no reported cases of skin cancer.

Friedman, et. al.² explored 105 commonly used drugs for possible carcinogenic effects. Among these drugs studied was oxybutynin (mostly prescriptions for oral formulations as per Dr. Raffaelli's personal conversation with Dr. Friedman). The authors did recommend further evaluation of eight drugs for a dermal carcinogenicity signal but oxybutynin was not one of them. See Dr. Raffaelli's review for more details.

During the review of this Rx-to-OTC switch application, many discussions of the data related to the carcinogenicity question involving the Division of Urologic and Reproductive Products (DRUP), the Division of Nonprescription Clinical Evaluation (DNCE), the Offices of Drug Evaluation III and IV, the Carcinogenicity Assessment Committee (on September 14, 2012) and Dr. Susan Walker, Director of the Division of Dermatology and Dental Products, have led to the recommendation that 2-year dermal carcinogenicity studies in rodents are not required to support the Rx-to-OTC switch of the Oxytrol TDS. The OTC labeling for the Oxytrol TDS will have instructions to rotate application sites among the abdomen, hips, and buttocks.

Oxytrol is a Pregnancy Category B drug, as are many approved OTC products. There are no adequate and well-controlled studies in pregnant women. The codified Drug Facts pregnancy labeling warning (21 CFR 201.63) proposed by the applicant, "**if pregnant or breastfeeding, ask a health professional before use**" seems reasonable to support the safety of the OTC TDS, if approved.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology studies required for this submission. The clinical pharmacology data for this submission was the same as that which supported the approval of the prescription NDA.

6. Clinical Microbiology

There were no microbiology data or reviews associated with this application.

7. Clinical/Statistical-Efficacy

There were no new clinical efficacy studies submitted for this OTC switch application. The two clinical efficacy studies submitted to support the prescription approval enrolled both men and women (predominantly women) and the population was skewed towards the elderly although the range was 23 – 88 years. The concurrent medical history in the enrolled

population was representative of the medical problems that occur in older people in that 55% had a history of cardiovascular disease and/or head/ears/nose/throat disease, 64% had a history of gastrointestinal disease, and about 84% had a history of musculoskeletal disease.

Studies demonstrated a significant decrease ($p < 0.05$) in the number of incontinence episodes and a significant increase ($p < 0.05$) in urinary void volume compared to placebo. One study also demonstrated a significant decrease in daily urinations. The clinical trial data supported that the Oxytrol TDS is efficacious by 2 weeks of use, so the advice on the proposed OTC label to stop use and ask a doctor if symptoms do not improve after 2 weeks of use is reasonable. Refer to the review by Dr. Donald McNellis for a more detailed description of the data that supported the efficacy of the Oxytrol TDS.

Some patients in the studies experienced improvement in symptoms that were clinically meaningful to them; others did not. As with any drug approved to treat clinical symptoms, an OAB sufferer needs to try the medication to learn if it will work for her. This is the case whether oxybutynin is a prescription product or an OTC product.

8. Safety

Social Science Studies:

Please refer to the Social Science Review by Barbara Cohen for a detailed analysis of the label comprehension studies and the self-selection studies performed to support this NDA.

Multiple label comprehension and self-selection studies were conducted in subjects of normal and low literacy to develop a well understood label to be used for the CONTROL actual use study and ultimately for the marketed product. The results of these studies, led to modifications of the label to improve areas where the testing indicated that improvement was needed, such as making the label pink do dissuade men from using the product and modifying a silhouette of a woman that was on the principal display panel (PDP) to discourage use by pregnant women.

Label Comprehension Studies:

Pivotal LCS:

The pivotal LCS was a multicenter study conducted in three cohorts of women:

Cohort 1: 472 females ≥ 18 years old with self-reported OAB, general population

Cohort 2: 120 females ≥ 18 years old with self-reported OAB, low literacy augmentation

Cohort 3: 160 females ≥ 44 years old with self-reported risk of diabetes

Cohorts 1 and 2 responded to identical questions about OAB symptoms and labeled warnings to assess their comprehension of the information presented on the label. Cohort 3 responded to questions related to two diabetes warnings: family history and excessive thirst. The applicant did not assess comprehension of two other diabetes warnings, “extreme hunger” and “increased tiredness.” (I do not appreciate the value of including such a nonspecific symptom as “increased tiredness” in the Drug Facts label and would recommend that it be removed.)

Results:

Table 1 shows the results for Cohorts 1 and 2 for medical issues thought to be of higher clinical concern.

Table 1. Results of for Cohorts 1 and 2 for Medical Issues of Higher Clinical Concern (Target Threshold for Success for Lower Bound of 95% Confidence Interval = 90%)

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: CDTL Review

Both cohorts understood the allergy warnings well. The narrow angle glaucoma warning was understood least well. As the reviewers point out, this was a general cohort and not a cohort that had glaucoma who was tested for comprehension. That latter cohort may have had a better understanding of this warning. A glaucoma warning is present on many OTC products that have been approved and marketed for decades and a safety concern related to this warning has not emerged. I think that the glaucoma population could be best served by mirroring the warning that is on other OTC products with anticholinergic effects (such as antihistamines), rather than the specific one regarding “narrow-angle” glaucoma that was tested for this product.

Because of reduced comprehension in this pivotal LCS and also some confusion in the actual use study (CONTROL) related to the issue of urinary and gastric retention, the applicant has proposed labeling modifications to clarify that a doctor should have diagnosed these conditions. This seems like a reasonable approach to me.

Table 2 provides the results for medical issues thought to be of lesser clinical concern.

Table 2. Results for Cohorts 1 and 2 for Medical Issues of Lower Clinical Concern (Target Threshold for Success for Lower Bound of 95% Confidence Interval = 85%)

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: CDTL Review

Consumer identification of OAB: The target threshold for success for the lower bound (LB) of the 95% confidence interval was 85%. Ms. Cohen (see page 12 of her review) notes that there was a significant difference in comprehension when comparing the normal literates from Cohort 1 with the low literates from Cohorts 1 and 2 (88% vs. 71%). Also, this question elicited the largest percentage of “don’t know” responses in the survey.

Ms. Cohen and Dr. Furlong both recommended that to assist low literate consumers to better appreciate the concept that symptoms should be present for at least three months prior to using the TDS, it might be helpful to emphasize this with formatting changes to the label to emphasize the words “at least.” I agree with them.

The subjects in Cohort 3 scored at 83% (lower bound) on the issue of family history of diabetes and at 82% (lower bound) on the issue of excessive thirst. From a clinical perspective, I think that the issue of excessive thirst was the most important concept to test regarding diabetes. I think that this plus the criterion of needing to have had symptoms for at least 3 months duration should create a safety net for new diabetics to enable them to make a proper self-selection decision regarding use of the Oxytrol TDS. If they do decide to try the product, I agree with Dr. Furlong that their lack of success with the patch may drive these women to a doctor sooner which may lead to an earlier diagnosis of their new onset diabetes. This would be a good thing.

Other Label Comprehension Studies Conducted earlier than the Pivotal LCS:
For details regarding the other LCS studies that were performed refer to Ms. Cohen’s review. I will point out a few results from some of these studies.

LCS #92101 demonstrated that comprehension of:

- The different urinary tract symptoms was good (89 – 94% LB of 95% CI)
- Wearing one TDS at a time was high (98% LB)
- Wearing the first patch for 4 days was high (96% LB)

- Wearing the second patch for 4 days was high (97% LB)
- The “stop use and ask a doctor” conditions was good (85% - 96% LB)

LCS #92099 demonstrated that among OAB sufferers there was generally good understanding of the diabetes family history and thirst warnings that were also tested in the pivotal LCS.

LCS #92062 demonstrated 93% comprehension among normal literacy subjects and 83% comprehension among low literate subjects that a doctor should be consulted if pregnancy might be causing the OAB like symptoms.

Self-Selection Studies:

SSS #10054 was a multicenter study among pregnant women with OAB symptoms. The general population cohort had 308 subjects and the low literacy cohort had 127 subjects. The study participants had to recognize that urinary frequency could be an early sign of pregnancy and that they should ask a health care provider before using Oxytrol if they were pregnant or nursing. The normal literacy cohort scored 88.3% (LB 84.2%) and the low literacy cohort scored 63% (LB 54%). Following this study, the applicant replaced an image of a woman wearing a tent-like dress on the PDP of the tested label with a woman with a more defined narrow waistline. Ms. Cohen stated that visual icons may help with comprehension among the less literate and she thought that the revised icon was a significant improvement over the one on the tested label. I agree with her and Dr. Furlong that this appears to be the case.

SSS #92061 was a multicenter study among 354 general literacy men and 217 low literate men with OAB symptoms. Ninety-two percent of general literacy men (LB 88.1), with nearly identical scores for the low literate men, self-selected correctly not to use the product. The target threshold for this study was 90% The PDP on the labeling tested was pink and contained an image of a woman.

SSS #2008-19 was the first self-selection study conducted, was done with an early version of the label, and had methodological flaws as described by Ms. Cohen in her review. The thing to point out about this study is that self-selection decisions were compared with a physician’s diagnosis which included a pelvic examination and laboratory testing. Of subjects agreeing to a physical examination, 89.4% of normal literates and 91.2% of low literates made a correct self-selection decision. Among those who did not, there were five with microscopic hematuria (ages 31, 44, 48, 65, and 74 years), four of whom had concurrent OAB.

After a careful review of the consumer data from the LCSs and SSSs, Ms. Cohen provided her recommendations for further enhancing the final label that the applicant proposed in the NDA. Dr. Furlong considered the recommendations and provided her point of view. Please see their reviews. I have the following thoughts:

- I agree that it makes sense to emphasize “at least” in “You may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months” under the “Uses” section of the Drug Facts Label. I agree that this may help people better understand the 3-month minimum duration of OAB symptoms recommended before using Oxytrol for Women®.

- Dr. Cohen made recommendations on placement of the information about a family history of diabetes. Advisory committee members suggested that this information may not be necessary on labeling for a variety of reasons (i.e., not necessarily predictive of developing diabetes, may not alone generate screening for diabetes in a woman who presents with OAB). I agree that this information is unnecessary on the label and think that removing it may enhance the readability of this already crowded label without removing important information.
- I agree that the revised female silhouette proposed by the applicant is an improvement over the one on the label that was tested in the self-selection study that focused on pregnancy. I think this icon may be further enhanced by putting a belt around the waist of the female silhouette. I agree with Dr. Furlong's analysis that the pregnancy warning on this Pregnancy Category B drug is adequate.
- I agree that the data have supported adequate decision making regarding men. The product is approved for use in men as a prescription product to treat OAB, so there is no inherent reason why men cannot use it for this condition OTC. The OTC product was designed to avoid the small risk in men with prostate hyperplasia of developing urinary retention. This risk is especially small because the drug only increases the urinary volume by approximately one tablespoon and, I agree with Dr. Furlong that if it were to occur, it would not be a life threatening event and might even hasten the diagnosis of previously undiagnosed prostate disease, which would be a good thing.

Actual Use Study (CONTROL):

Please refer to Dr. Raffaelli's review for a detailed description of this clinical trial. This was an open-label, single arm, multicenter actual use study conducted under simulated OTC conditions. The study provided uncontrolled safety data from women who were using a product label similar to the one that was ultimately proposed by the applicant for marketing. The label used was the product of refinement after multiple label comprehension studies and self-selection studies. The primary endpoint of the CONTROL study was the proportion of verified TDS users who did not stop use when they developed new or worsening symptoms over all verified users. The primary endpoint had a prespecified threshold of < 5%.

Interested women purchased Oxytrol for Women®. A pharmacist took a medical and demographic history and 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, who otherwise would have been ineligible to use the product as per labeling were allowed to purchase the product and use it. Subjects kept a medication diary, the final one of which was collected at week 15, and were also interviewed by telephone at weeks 3, 7, and 12. They were allowed to purchase up to 24 boxes of the product (96 patches) so that they had opportunities to overuse the product and this behavior could be evaluated. A urinalysis was performed at the end-of-study visit (EOS).

Results:

Of the 1069 women who decided to purchase the drug, 839 (78.5%) had some ineligibility for using the drug as per the Drug Facts label on the study drug. However, 87.1% had OAB symptoms for at least three months, as per the label. Twenty-seven women were excluded by the investigators for medical conditions listed in the paragraph above. A total of 785 women

reported using the TDS but diaries confirmed use by 727 women (called verified users). As Dr. Furlong and Dr. Raffaelli note, since subjects during the label comprehension and self-selection studies understood the labeling when asked to read it, it appears that large numbers of subjects chose to ignore the labeling or did not read it carefully.

The study met its primary endpoint with a result of 3.4% (25 of 727 verified users). There were no marked differences based upon age, race, or literacy. The statistical reviewer analyzed the data and did not identify any issues to preclude approval. Dr. Raffaelli determined that 25 (17.7%) subjects of the 141 verified users who had new or worsening symptoms failed to stop use. Looked at inversely, 82.3% of users who should have stopped use actually did.

There were 152 users of 727 who used a TDS for more than 4 days or used more than one TDS simultaneously. The reviewers note that this number was predominately driven by those who used that patch longer than 4 days. This should not be a safety concern. Twenty-two verified users applied more than one patch at a time. The reasons provided at the end of study interview were either forgetting to remove a patch or trying more than one to help with symptoms. This behavior could occur whether the product was a prescription product or an OTC product.

There were a total of 975 AEs reported by 519 users. The majority of these (63.2%) were considered to be unrelated to Oxytrol. **Table 3** lists the most common AEs reported in the AUS by age. Overall, there were no differences in adverse events related to age.

Table 3. Most Commonly Reported Adverse Events 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: CDTL Review

There was one death during the CONTROL study due to viral pneumonia. This death was determined to be unlikely related to Oxytrol. Of users, 35 of 785 (4.5%) reported SAEs; of nonusers who provided data 8.6% reported SAEs. One of the SAEs reported by a user was considered possibly related to Oxytrol. This was a patient report of difficulty awakening from anesthesia that resulted in moving her from a clinic to a hospital. Those subjects who discontinued use due to an adverse effect totaled 152.

Please see Dr. Raffaelli’s review and Dr. Furlong’s review for a detailed analysis of adverse event of special interest. In summary, a lack of attention to label warnings for UTI, diabetes,

and urinary retention did not result in SAEs related to these diagnoses. No cases of bladder cancer were diagnosed either among those who were included in or excluded from the trial. There were no true allergic reactions reported. Local skin reactions were common. There were no serious anticholinergic effects reported but because dry mouth and constipation were not infrequent, the reviewers felt that these AEs should be added to the OTC product label and I agree with this recommendation. Twenty-nine subjects reported dizziness/somnolence. I agree with the reviewers that these warnings should also be on the Drug Facts label because of their potential to lead to accidents. There were no reports of glaucoma during the trial. A discussion of the glaucoma warning is on page 7 of this summary review under the section on label comprehension studies. There were no reports of gastric retention or urinary retention. It was difficult to attribute falls and accidents that occurred during the study to drug use.

Dr. Ryan Raffaelli and Dr. Lesley-Anne Furlong differed with regard to his recommendations that the OTC label should have warnings against use for those with ulcerative colitis, myasthenia gravis, gastroesophageal reflux disease and esophagitis. I agree with Dr. Furlong that these do not need to be on this label based upon our longstanding experience with the safety of other anticholinergic drugs OTC and agree with the rationale that she provides for her thinking. Likewise, I disagree with Dr. Raffaelli and agree with Dr. Furlong that the data do not support that a cardiac warning is needed on the Oxytrol TDS label.

Safety Data from other Sources:

- Clinical trial data from 19 trials reviewed for the prescription NDA, including exposure of 663 patients and 83 healthy volunteers to one or more applications of Oxytrol (1 day of use – 428 days of use)

The oxybutynin TDS was reasonably well-tolerated in the clinical trials. The acceptable safety profile led to the prescription drug approval. Refer to Dr. McNellis' review for details. In brief, the clinical trial data demonstrated that the most frequent adverse effects associated with oxybutynin patches are skin irritation (primarily pruritis) and anticholinergic effects such as dry mouth, constipation, and dizziness. Application site erythema was reported as were headaches. These adverse effects were generally mild. Of the 98 drug-related adverse events that were graded as severe, 64 (65%) were application site-related and others were anticholinergic effects such as dry mouth, constipation, and dizziness.

There were no deaths reported in the clinical trials. Thirty-seven subjects experienced 47 serious adverse events (SAEs), none of which was considered to have been related to study drug.

- A summary of all postmarketing safety information from 2003 until Feb 25, 2011. These data cover an estimated 270,000 patient-years of use in the United States and over 130,800 patient-years of foreign use. Included are 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).

For a detailed review of the postmarketing safety database, refer to Dr. Raffaelli's and Dr. McNellis' reviews. IMS data estimate that there have been global sales of [REDACTED] (b) (4) with almost [REDACTED] (b) (4) Oxybutynin TDSs sold in the United States and approximately 400,000 patient-years of treatment. This reflects substantial time and extent of product use.

Analysis of the safety data resulting from this vast history of product use shows that adverse events are relatively few in number and that they are similar and consistent with the adverse events reported during the Phase 3 clinical trials that supported the prescription approval. The pattern of adverse events reviewed for the OTC switch of the oxybutynin patch was consistent with the prescription product labeling. This prescription labeling was updated in October 2012 to include a new somnolence warning under central nervous system effects. The warning is now:

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

Since the approval of the Rx product, the only other warning update to the oxybutynin labeling has been an angioedema warning (January 2011). This adverse event has been infrequently reported with use of the oral formulations of oxybutynin but has not been attributable to the Oxytrol TDS; however, it was included on the prescription labeling for the patch as "class labeling."

- Watson Pharmaceuticals' Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin (MATRIX) study, a community-based, open-label phase 4 study evaluating quality of life changes and tolerability over 6 months of prescription Oxytrol use by 2,881 adult OAB patients.

This study was performed voluntarily by Watson Pharmaceuticals, the holder of the prescription Oxytrol TDS NDA. Most enrollees were female and the median age was 63 years. Half of the subjects completed the 6 months of treatment. There were no study-related deaths and only one of the 168 subjects reporting SAEs had an event (a urinary tract infection) that was attributed to the study medication by the physician.

Of the ten subjects who reported urinary retention, all were considered nonserious and drug-related with the exception of one case. This one case was of an 86-year-old woman with chronic urinary retention. This was considered a SAE, but it was not considered drug-related. The woman had an ultrasound established diagnosis after she had used Oxytrol for almost 5 months.

Of interest, during this study 67 subjects reported 82 UTIs in this physician-managed population. Thus, among the 2881 subjects approximately 2% experienced a UTI and one was considered to be study drug related. So, as Dr. Furlong commented, UTIs occurred in the OAB population. A relationship with study drug use was rare. SAEs secondary to UTIs and attributable to product use were rare in this physician managed population. Similar results

were seen in the CONTROL study which was conducted in an OTC-like setting. I agree with the DNCE and DRUP reviewers that it is unlikely that OTC Oxytrol TDS use would cause a clinically meaningful delay in the diagnosis of urinary tract infections.

In this physician managed MATRIX population, there was one case of prostate cancer diagnosed in a man who had used Oxytrol for over 5 months. The percentage of Oxytrol users reporting SAEs in the MATRIX trial was 5.8% and in the CONTROL trial was 4.5% respectively.

9. Advisory Committee Meeting

On November 9, 2012 a meeting of the Nonprescription Drugs Advisory Committee was held to discuss the partial OTC switch application for the Oxytrol TDS. In a 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? However, some members indicated that more information in labeling might have persuaded them to vote “yes.”

During discussions, two members who voted “no” expressed their concern for 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. They also expressed a second concern related to the lack of information on the OTC label about behavioral techniques for managing OAB. A third concern raised was the possibility of a delayed diagnosis of bladder cancer or bladder cancer in situ in an OTC setting.

Dr. Furlong and Dr. Raffaelli recommended labeling the product to “ask a doctor if you are over 64.” I disagree with this recommendation, because it would deny the OTC availability of the drug to the population most likely to benefit from it. Also, in the clinical trials, large numbers of elderly patients benefitted from this medication to treat their OAB symptoms and experienced few adverse CNS effects of concern. Oxytrol TDS, if approved, will not be the only drug with anticholinergic effects OTC; many have been available for close to half a century with a favorable benefit-risk ratio. It is not at all clear that people who are taking the Oxytrol patch via prescription are any better informed about the potential risks of using more than one drug with anticholinergic effects than the OTC consumer would be. After careful consideration, I think that enhanced language on the Drug Facts Label regarding the risks of CNS effects for Oxytrol could adequately address this safety concern. The addition of a Consumer Information Leaflet (CIL) to provide information on behavioral techniques for managing OAB could address the concerns brought forth by some NDAC members.

Dr. McNellis thoughtfully addressed the issue of use of Oxytrol TDS in patients with undiagnosed bladder cancer or bladder cancer in situ in his review. He wrote that symptoms relatable to bladder cancer appear to differ significantly enough from overactive bladder. He comments that bladder cancer largely presents with hematuria (80 – 90% of cases) and that mostly this is gross hematuria, with microscopic hematuria responsible for the initial presentation in only about 2% of cases. Gross hematuria would assist consumers in identifying

their problem as a cancer and distinct from the condition of overactive bladder. Dr. McNellis notes that irritative symptoms such as increased frequency and urgency are the next most common presentation for bladder cancer but that the cause of the irritative symptoms in bladder cancer differs from that in OAB. The antimuscarinic action of oxybutynin is not apt to have efficacy in reducing the cancer induced irritative symptoms. (Refer to Dr. McNellis' review for a nice discussion of the risk of bladder cancer among women who might present with OAB and the pathophysiology of the symptoms in that condition.) Because it is not likely that Oxytrol TDS would work in the small number of women with bladder cancer who might try it, any delay in diagnosis of the bladder cancer should be short and not likely to have a significant impact on the course of the disease. The proposed OTC product is labeled to direct people who a doctor who have not achieved relief within two weeks. It is possible that a failure to respond to the Oxytrol TDS would actually drive people to the doctor for an evaluation.

As Dr. Furlong points out, annual preventative visits are covered for all elderly Americans by Medicare. The marketing around Oxytrol for Women®, dissatisfaction with the drug if it does not work for the symptoms, and mentioning its use to a doctor might prompt further screenings, or initiate a discussion regarding embarrassing bladder symptoms that people are often reluctant to discuss. This might lead to more cases of bladder cancer being diagnosed. Additionally, as Dr. Furlong notes, bladder cancer is three times more common in men than in women, so the population targeted by Oxytrol for Women® is less at risk. I agree with the review team a small risk of a short delay of diagnosis of bladder cancer should not block the approval of Oxytrol for Women®, a medication that could help many OAB sufferers to feel better.

One advisory committee (AC) member raised a concern about parents medicating young children for enuresis. Refer to Ms. Cohen's review to see that the age limit was highly understood (95% - 98% LB) among the three cohorts in whom it was measured in the initial LCS. These study subjects responded correctly to a question about whether the product could be used in an 8-year-old. I do not think an expanded warning against use in children is needed.

Some members expressed concerns about the target threshold in the consumer studies for use in diabetics being too low at 85%, concerns about use in men, and about the pregnancy self-selection study with regard to low literates. I have provided my thoughts about the data with regard to pregnancy and men above. I also think that the diabetes warning has been adequately covered. Furthermore, if people have had urinary frequency symptoms for 3 months due to glycosuria and have not yet seen a physician, if they try the patch (which shouldn't work in this situation) this may hasten their choice to seek medical care.

10. Pediatrics

This drug product is targeted to adult women and is not to be used for children. The efficacy and safety in the pediatric population has not been established. The LCS data support that consumers understand that the product is not to be used in children.

This partial prescription to nonprescription switch application does not trigger the need to address the Pediatric Research Equity Act because Oxytrol for Women® does not contain a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

At the time of this review, labeling negotiations were still in process with the applicant. My comments on labeling content are peppered throughout this review.

DMEPA has approved the proprietary name Oxytrol for Women®. I have no concerns with that name either. I disagree that the female silhouette looks like a “P” as the DMEPA reviewer posits and I agree with Dr. Furlong that there is no problem there. DMEPA conveyed their safety concern to the applicant about the visibility of the ink on the TDS; however, no safety reports on the prescription TDS have prompted this concern. At this time it is theoretical. On December 3, 2012, the applicant made a post-marketing commitment to change the text on the backing film to a darker ink within one year from the date of approval.

I concur with the recommendations in Maria Ysern’s DNRD labeling review. They are provided to bring the labeling into compliance with the regulations under 21CFR201.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I recommend that this NDA be approved pending completion of satisfactory labeling negotiations.

Risk Benefit Assessment

To be an OTC drug, a product must meet the regulatory standards of the Code of Federal Regulations 21CFR 310.200 which states:

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

Therefore, for a drug to be OTC, the labeling must convey the information needed to use the product safely and effectively in the absence of a healthcare practitioner. Demonstrating that a product label can result in appropriate use is consistent with the tenet that the Agency has applied in the past and continues to apply when determining whether or not a product can be over-the-counter.

No new efficacy or safety concerns for the Oxytrol TDS were raised during the review of this application. After review of the benefits and risks associated with the Oxytrol TDS from preapproval and postmarketing databases and the data from label comprehension, self-selection and actual use studies, I agree with the review team that the applicant has shown that Oxytrol for Women®, with some updates in labeling to address:

- CNS adverse effects such as somnolence and dizziness,
- Dry mouth, constipation,
- An emphasis on “at least” three months of symptoms under Uses,
- Behavioral methods to treat OAB provided in a Consumer Information Leaflet
- The potential for CYP3A4 interactions

meets the regulatory standards of an OTC drug.

I think the glaucoma warning should be simplified to be consistent with glaucoma warnings on other OTC products. The kidney stone warning and the diuretic warnings on the proposed OTC label are not on the prescription label. We do not have data to justify that they should be on the oxybutynin labeling and they should be removed. I also recommend removing “extreme tiredness” and “family history of diabetes in your immediate family” from the label because I think they clutter it with information that is not particularly useful.

I think the female image on the PDP could be redrawn to show even a more defined waistline than currently exists. This may further address any concerns about pregnant women self-selecting to use the product.

I agree with the reviewers that the LCSs, SSSs and AUS support that women who will use Oxytrol for Women® are able to make a favorable risk-benefit decision related to use of this product. In the AUS, even when consumers took the medication in the absence of heeding a warning, the safety data were not of concern. I think this medication, if OTC, can provide a safe and effective option for many women who are suffering with OAB to help themselves to feel better and thus improve their quality of life.

Potential safety concerns for this OTC switch that were raised at the November 2012 Advisory Committee meeting were primarily related to possible delay in diagnosis of other medical conditions that could lead to significant clinical consequences. I concur with the reviewers that it is unlikely that use of Oxytrol will result in a clinically significant delay in seeking medical treatment of non-OAB medical conditions and that it is possible that these consumers will seek medical advice sooner if the Oxytrol TDS does not result in clinical improvement.

For all of the reasons described above I conclude that the risk/benefit assessment favors approval of the partial OTC switch for Oxytrol for Women® for treatment of OAB.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None

- Recommendation for other Postmarketing Requirements and Commitments
The applicant made a post-marketing commitment to change the text on the backing film of the TDS to a darker ink within one year from the date of approval.

References:

1. Brown, JS, Vittinghoff E, Wyman JF, et al. Urinary incontinence: does it increase risk for falls and fractures? Study of Osteoporotic Fractures Research Group. J Am Geriatr Soc 2000;48:721-5.
2. Friedman GD, N Udaltsova, J Chan, CP Quesenberry Jr, LA Habel, 2009, Screening Pharmaceuticals for Possible Carcinogenic Effects: Initial Positive Results for Drugs not Previously Screened, Cancer Causes Control 20: 1821-1835.

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

/s/

ANDREA LEONARD SEGAL
12/21/2012