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RESEARCH**

APPLICATION NUMBER:

202211s000

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 01/23/2013
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, ODE-IV
To: File, NDA-202211
Subject: Approval of NDA 202211, Oxytrol for Women[®] (oxybutynin transdermal system), as an over-the-counter treatment of overactive bladder in women

This is the ODE-IV Deputy Office Director's memo to concur with the approval of this NDA, as recommended by the Division of Nonprescription Clinical Evaluation (DNCE). This application was jointly reviewed by the Division of Reproductive and Urologic Products (DRUP) in the Office of Drug Evaluation III (ODE-III), approval is also recommended by DRUP and concurred by ODE-III. Oxybutynin is an anti-cholinergic agent approved as a prescription drug to treat overactive bladder (OAB)¹ for both men and women in 1998 (oral tablets) and in 2003 (transdermal system, or TDS). Oxybutynin TDS is formulated as a patch to deliver 3.9 mg/day of oxybutynin for transdermal administration over 3-4 days. This NDA application is for partial switch from prescription to over-the-counter (Rx-to-OTC) use for women only because of the concern of prostate related complications associated with the OTC use in men. Oxytrol for Women[®] will be the first OAB treatment available as an OTC drug product.

Overall, the data submitted in this application support the approval of this partial OTC-to-Rx switch. As summarized in the DNCE Division Director's memo by Dr. Andrea Leonard-Segal, reviews by relevant disciplines and facility/data inspections have all been completed. There are no outstanding issues identified in the reviews or inspections that may preclude the approvability of this application². This application does not trigger requirements to meet Pediatric Research Equity Act. The sponsor has reached an agreement with the Agency on the content of the final labeling.

Studies to Support OTC Use

No new controlled clinical trials were considered necessary for this switch application as clinical efficacy and safety have been established for the prescription product. For non-clinical toxicology, the current review team deliberated the need of dermal carcinogenicity study (not performed for the Rx approval) and correctly concluded not to require now (see summary by Dr. Leonard-Segal in her review). Safety data in pre-approval clinical trials and postmarketing experience/studies for the Rx product were also reviewed for this submission.

The sponsor submitted results of an actual use study (AUS), Consumer Trial of Oxytrol (CONTROL) in this application, which provides the major support for the effective and safe use of Oxytrol TDS as an OTC drug. The sponsor also tested various versions of OTC labeling in an iterative process with 6 labeling comprehension studies (LCSs) and 3 self-selection studies (SSSs). Major regulatory and clinical issues of this NDA, as raised in the review of these studies

¹ With symptoms of urinary frequency, urgency and incontinence (see medical reviews).

² Some earlier CMC concerns of approvability noted in Dr. Furlong's Cross-Discipline Team Leader (CDTL) review have been resolved in a CMC addendum, as also noted by Dr. Leonard-Segal in her review.

and discussed in the Advisory Committee (AC) meeting of November 9, 2012, are discussed below.

Self-Diagnosis of OAB

The symptoms of OAB, including urinary frequency, urgency and incontinence, are obvious to the patients as shown in the labeling/selection/usage studies. As it is a relatively benign condition usually diagnosed by exclusion, sufficient waiting period should be allowed for evaluations of other etiologies for the symptoms, as recommended by the reviewers (at least 3 months). However, it is not clear whether such instruction will encourage the patients to presume the diagnosis of OAB and not to seek professional attention for 3 months. This minor concern has not been tested, but should not be an approvability issue. Otherwise, the diagnosis-related language in the proposed labeling has been tested in the LCSs and SSSs, and deemed acceptable by the reviewers. Color and graphic features will be used to emphasize the use in women only.

The major concerns about self-diagnosis, as raised in the FDA reviews and at the AC meeting, involve potential delay of diagnosis/treatment of the following more serious conditions that may present with mimicking symptoms.

- **Bladder cancer**

Both the reviewers and the Advisory Committee devoted considerable effort deliberating whether OTC use of oxybutynin will delay the diagnosis of bladder cancer because hematuria may not be detected without a urinalysis. It was actually one of the major reasons some AC members voted against approval for the switch³. The FDA reviewers⁴ reason that bladder irritation alone is not the usual presentation for bladder cancer, which is more common in elderly men, and the delay in diagnosis will be short because such symptoms will not respond to anti-cholinergic agents. The conclusion reached by them that this drug should pose no serious safety concern is thus essentially correct. Nevertheless, while oxybutynin is not likely to be effective in this setting, the real concern is that some, albeit very few, may respond (due to placebo effect?) and thus delay medical attention. Such patients must be very rare (<10% presented without hematuria x small % who may respond to oxybutynin).

- **Diabetes**

While missing underlying diabetes is also a concern of some AC members, the delay for the correct diagnosis will be short-lived because oxybutynin treatment will not likely be effective in treating diabetic urinary frequency. And even for those very few who might respond, postponing the proper management for diabetes for several weeks will not cause serious harm to these patients whose major symptom is urinary frequency. Warnings on diabetes as the cause of urinary frequency in general and in women with diabetic risks have been adequately tested in LCSs and thoroughly reviewed by the clinical team.

³ The Advisory Committee voted 6-5 against approval. Reasons for objection to approval are discussed in the reviews and in this memo; the concerns can be safely dismissed after careful consideration or adequately mitigated by labeling approaches.

⁴ See summary by Dr. Leonard-Segal and reviews by the medical teams in DNCE and DRUP, esp. the detail analysis by Dr. McNellis of DRUP.

- **Urinary tract infection (UTI)**

The usage study showed that UTI is a common co-existing condition in the OAB patients. As noted by Dr. Furlong, acute UTIs are usually painful, and would not likely be tolerated for months without seeking professional attention. The medical reviewers concluded that, from the results of the CONTROL trial, most consumers do not confuse UTI with idiopathic OAB, nor does it seem that diagnosis of UTI is likely to be delayed.

- **Pediatric enuresis**

One AC member was concerned about parents medicating children for enuresis. This risk can be minimized by the labeling, as the age limit in the proposed labeling was highly understood at 95-98% level in the LCS. While labeling comprehension may not translate into complete behavioral compliance, Dr. Leonard-Segal's conclusion is concurred that no stronger warning against use in children is needed.

- **Pregnancy**

Although urinary symptoms may develop during early pregnancy, delay in diagnosis of pregnancy is not going to be too long or harmful. The safety concern is instead the mis-use of oxybutynin during pregnancy (see below).

Self-Administration with Oxybutynin TDS

Application of the TDS patch to the skin is straight forward and requires no extensive instruction or learning. The following issues related to self-administration have been discussed by the reviewers and addressed in the proposed labeling.

- **Application of TDS**

To minimize acute local irritation and chronic pathological changes (see notes above on dermal carcinogenicity), the labeling includes instruction not to apply the TDS at the same sites successively.

- **Overuse**

The Advisory Committee argued that the labeling should advocate behavioral change as a preferred approach to manage OAB, before administration of the oxybutynin TDS. Reference to behavioral techniques is now included in the proposed consumer information leaflet (CIL). Since behavioral methods and life style changes are already well-known to the OAB patients, and the professional societies have no recommendation on the order of different approaches (see Dr. Furlong's review), over-emphasizing behavioral changes is not necessary.

It was observed in the usage study that some patients used more than one patch at the same time, which is not surprising for OTC products and has not caused any safety problem. The pharmacokinetic data indicate that maximum systemic exposure from such mild over-dose with two patches (some left the additional patches on for longer than the specified period) will still be lower than the maximum recommended oral dose of 30 mg⁵.

- **Misuse**

Inappropriate use in certain conditions, such as pregnancy, is a potential concern. Warning on pregnancy was tested in one LCS and in one SSS of pregnant women. In

⁵ See clinical pharmacology review of NDA 21351 and labeling of the Rx TDS product.

addition to the Category B designation, a modified silhouette of a woman to discourage use by pregnant women will be on the principal display panel (PDP).

As noted above, leaving the patch on the skin site for longer than 4-5 days can happen, but other than local irritation, it should not be a serious safety concern.

Self-Management of Adverse Events

No new signals of toxicity were detected in the review of post-marketing experience and a study⁶ conducted post-approval. Adverse events in the OTC usage study seem to be mostly mild, non-serious and tolerable or manageable (see medical reviews). Specific safety issues in OTC use that have attracted attention from the Advisory Committee and the reviewers are summarized as follows⁷:

- **Urinary retention**

Despite that inability to completely empty the bladder was often neglected as an ineligibility for the usage study, no confirmed acute urinary retention has been reported in the study. This observation is consistent with the rarity of the event in the large post-marketing experience/study and literature (see Dr. Furlong's review). For most patients, oxybutynin increases the urinary volume only very modestly (one tablespoon, see Dr. Leonard Segal's memo). Warning on urinary retention has been tested in the LCSs and will direct patients to professional medical care if this event occurs.

- **CNS effects**

Two AC members voted against approval of this partial switch, citing safety concern of oxybutynin's CNS effects – dizziness & somnolence. The elderly are especially vulnerable as they usually carry substantial geriatric burdens, including cognitive impairment, likely on drugs with adverse interaction, and prone to suffer injuries from the CNS effect due to osteoporosis and anti-coagulation. The DNCE medical reviewers share this concern and note that the warning on CNS effects has been recently upgraded in the Rx labeling because of sporadic reports of related adverse events. The AC members and the reviewers recommend that the elderly patients (e.g., over 64) should be advised to consult their physicians first. However, as Dr. Leonard-Segal pointed out, such age restriction is unnecessary as the CNS effects of oxybutynin were not prominent in the elderly subjects in clinical trials. The restriction would also defeat the purpose of this switch because the main age group that will benefit most from the OTC availability will be excluded. Instead, managing the risk with the enhanced language in the Drug Facts Label is preferred. Without specifying an age limit, the consumers are instructed to “ask a doctor or pharmacist” if they are taking other medications that also affect their CNS function (e.g., sleepiness, dizziness).

- **Glaucoma**

Narrow angle glaucoma is a common, labeled adverse event for many OTC anti-cholinergic agents. In the LCSs, warning on glaucoma was poorly understood in a

⁶ The MATRIX study (Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin) was conducted by Watson Labs in 2004-2005.

⁷ Dr. Furlong's additional comments on labeling in Section 12.4 of her review are concurred, except for the recommendation to add “ask a doctor” for patients over 64 (see CNS effects).

general cohort. It is conceivable that a different group of subjects who have glaucoma would have a better understanding of the warning. Further simplifying the language will also help improve the reading (delete “narrow angle”).

- **Other anti-cholinergic effects**

There is no new data to suggest that oxybutynin is significantly different from other anti-cholinergic agents with respect to the risk of adverse events due to anti-cholinergic effects. In this respect, dry mouth and constipation will be included as adverse events in the labeling.

Overall benefit/Risk of Oxybutynin for OTC use

As noted by Drs. Furlong and Leonard-Segal in their reviews, both the clinical setting of OAB and therapeutic effect of oxybutynin TDS make the drug a suitable candidate for OTC marketing. The feasibility for the consumers to manage OAB by themselves has been tested and demonstrated in the LCSs and SSSs in consumers.

While there are safety concerns about self-diagnosis of OAB, such risks can be mitigated or managed by the labeling approaches. The topical administration of oxybutynin TDS by the patients can be done without supervision and no serious complication is likely to occur in such use even some consumers may not comply with all the instructions in the labeling. Adverse events in patients using oxybutynin TDS appear mostly to be non-serious, self-recognizable and manageable with proper labeling.

The overall favorable benefit/risk ratio of the Rx product is thus maintained when oxybutynin TDS is used in the OTC setting.

Conclusions

Oxytrol for Women[®] is approvable as an OTC treatment for OAB in women only, with the final labeling as agreed upon between the sponsor and the Agency.

cc:

ORIG: NDA- 202211

Directors, ODE-III, ODE-IV

Directors, DNCE, DRUP

Deputy Director, DNCE

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

/s/

SHAW T CHEN
01/23/2013

Deputy Division Director Summary Review

Date	January 2, 2013
From	Audrey Gassman, MD
NDA #	202-211
Applicant name	Merck Consumer Care
Date of receipt of original submission	March 26, 2012
PDUFA goal date	January 26, 2013
Proprietary name/established name	Oxytrol for Women/oxybutynin transdermal system
Dosage Form/strength	Transdermal release system/3.9mg per 24 hours
Proposed Indications	Treats overactive bladder in women
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Lesley-Anne Furlong, MD
DNCE Medical Officer Review	Ryan Raffaelli, MD
DRUP Medical Officer Review	Donald McNellis, MD Suresh Kaul, MD
DNCE Statistical Review	Yunfang Deng, PhD Yan Wang, PhD
DNCE Social Science Review	Barbara Cohen, MPA
DNCE Pharmacology/toxicology Review	Cindy Xinguang Li, PhD
ONDQA Review	Sheldon Markofsky, PhD Carolyn Strasinger, PhD Terrance Ocheltree, PhD
DNCE Labeling Review`	Marian Ysern, IDS Ruth Scroggs, PharmD
ONDQA Biopharmaceutics	Tapash Ghosh, PhD Angelica Dorantes, PhD
DMEPA	James Schlick, RPh, MBA Todd Bridges, RPh Kellie Taylor, PharmD, MPH
OSI	Sharon Gershon, PharmD Susan Leibenhaut, MD Susan Thompson, MD

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DNCE= Division of Nonprescription Clinical Evaluation
DRUP=Division of Reproductive and Urologic Products
ONDQA = Office of new Drug Quality Assessment
DMEPA=Division of Medication Error Prevention and Risk Management
OSI=Office of Scientific Investigations

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1. Introduction

The original NDA submission (21-351) for oxybutynin transdermal system (hereafter referred to as the tradename Oxytrol) was approved based on two adequate and well controlled phase 3 trials (O99009 and O00011) in 2003. The clinical and statistical review teams reviewed data from these trials and concluded that they contained adequate efficacy and safety information to support the approval of Oxytrol for treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency (See Clinical Review dated February 7, 2003, and Statistical Review dated February 13, 2003).

For the current submission, the Applicant is seeking a partial over-the-counter (OTC) switch for the approved Oxytrol product (also referred to as “Oxytrol” throughout this review) for use solely in women (Oxytrol for Women). Although the prescription Oxytrol patch is approved for use in both men and women, the Applicant requested approval for the OTC product solely in women because of the potential for men with symptoms of overactive bladder to also have undiagnosed prostate disease. Oxytrol will remain a prescription product for men.

Analysis of the available postmarketing safety data for the prescription Oxytrol product did not reveal any new safety signals or concerns. A Nonprescription Drugs Advisory Committee meeting was held on November 9, 2012, to discuss the application to switch the prescription product to an OTC product for use in women. Safety concerns raised by committee members at that meeting will be addressed through product labeling and a new consumer information leaflet.

There are no outstanding clinical pharmacology, nonclinical toxicology, or chemistry, manufacturing and control (CMC) issues. OTC labeling for Oxytrol for Women was developed based on label comprehension studies and self-selection studies that were considered acceptable after review by DNCE. Labeling was submitted by the Applicant and is under negotiation. Both the primary DNCE and DRUP clinical review teams and

the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendation.

2. Background

Overactive bladder (OAB) describes a constellation of urinary symptoms that include urinary urgency, frequency and/or urge incontinence. These symptoms usually occur in the absence of obvious pathology, such as bladder outlet obstruction or genitourinary malignancy, and OAB is a diagnosis of exclusion. This condition has been reported as widespread and has a negative impact on quality of life, even after controlling for co-morbidities. The mainstay of treatment in the United States for overactive bladder is antimuscarinic therapy, and the most common antimuscarinic used for this purpose is oxybutynin. Oral dosages of oxybutynin, which include tablets and syrups, cause common antimuscarinic side effects that include drug mouth, constipation and cognitive disturbances. Because of these common adverse reactions, tolerance of and compliance with oxybutynin has been problematic for patients.

Oxytrol was developed by the NDA Applicant (Watson Pharmaceuticals, Inc.) as a transdermal system to improve patient compliance and tolerability with oxybutynin therapy (Reference IND #50489). It is believed that the oxybutynin transdermal system would improve antimuscarinic adverse reactions through lowering systemic blood levels of N-desethyloxybutynin, the metabolite believed to be associated with anti-muscarinic side effects. The Applicant also believed that the convenience of a twice a week transdermal system as opposed to daily oral medication would improve patient compliance. The original NDA submission (21-351) for the oxybutynin transdermal system (Oxytrol) was submitted on April 26, 2001. This submission sought approval of (b) (4) 3.9 mg/day and was supported by the results of one phase 3 study, study O99009. On March 26, 2002, the NDA received a Not Approvable letter due to several deficiencies. In response to the Not Approvable letter the Applicant took the following actions:

1. (b) (4)
2. They reanalyzed Study O099009, with the reanalysis including all missing diary data and removing all data related to Study Site #12. This was done as recommended by the Division of Scientific Investigations because of irregularities in the data obtained from this site.
3. They conducted a second phase 3 study (O00011), evaluating the efficacy of the 3.9 mg/day dose over 12 weeks in patients who had previously benefited from anticholinergic therapy.
4. They conducted two additional studies evaluating the cumulative skin irritation resulting from use of the 3.9 mg/day patch.

The Sponsor submitted a Complete Response to the Not Approvable letter on August 29, 2002. This response included the reanalysis of study O099009, the data for the new efficacy study O00011, and the requested skin irritation data. Upon review of these data, the Agency concluded that study O099009 demonstrated significantly greater improvement in both number of weekly incontinence episodes and micturition episodes

as compared to placebo. They also concluded that the newly submitted study O00011 demonstrated significant improvement in incontinence episodes, but not micturition frequency, as compared to placebo. Based on the submission of two successful pivotal trials, the DRUP clinical review team and statistical review team concluded that the results of these studies demonstrated adequate evidence of efficacy of Oxytrol in the treatment of overactive bladder. The clinical review team also determined that the submitted skin irritation studies were found to show acceptable skin safety, which was the single outstanding safety deficiency for this NDA. After the Agency's review of the Complete Response to the Non Approval action, Oxytrol at the 3.9 mg/day dose was approved for the treatment of symptoms of overactive bladder on February 28, 2003.

The original IND submission to support a switch of prescription Oxytrol to OTC status was discussed at a Type B PreIND meeting held on April 16, 2007 (Reference IND 74,288). The proposed indication for the OTC product was "treats overactive bladder" (b) (4)

(b) (4) Two other key meetings were held to discuss a proposed development plan and rationale to support the OTC switch:

- An End-of-Phase 2 meeting on October 13, 2009
- A PreNDA meeting on September 12, 2011

During these meetings, key components of the development plan, including design of the label comprehension study, self-selection studies and mitigation analysis criteria, were discussed. No new efficacy or safety studies were proposed. (b) (4)

(b) (4)
At the preNDA meeting held with the sponsor on September 12, 2011, further discussion of the format and content of the submission for the partial switch occurred.

The NDA submission for the partial OTC switch for Oxytrol (NDA 202211) was received on March 26, 2012, and filed on June 4, 2012.

3. Chemistry, Manufacturing and Controls

Oxybutynin is a racemic mixture, a white (b) (4) powder, and is practically insoluble in water. However the drug substance is freely soluble in ethanol, acetone, methylene chloride, and chloroform. The oxybutynin transdermal drug delivery system (TTDS) (also referred to as the Oxytrol patch) is designed to release oxybutynin gradually over a 4 consecutive day period. The system is a three layer matrix design consisting of a translucent backing film, an adhesive matrix and an overlapped-tab release liner that is removed prior to system application. Each system contains 36 mg of oxybutynin in an (b) (4) (b) (4). The only other excipient is triacetin which is used as a (b) (4). The oxybutynin transdermal system (Oxytrol for Women) will be an identical drug product to the currently approved drug product, Oxytrol, described in NDA 21-351. The system is designed to deliver approximately 3.9 mg/day.

The only notable change between the prescription Oxytrol submitted under NDA 21-351 and this partial OTC switch application for Oxytrol for Women (NDA 202-211) is the addition of a child resistant layer to the (b) (4) pouch (b) (4) (b) (4). The pouch material is the same as that described in Oxytrol NDA 21-351 in terms of the product contact materials.

After an initial review of this NDA submission, in a review dated November 16, 2012, the chemistry reviewer concluded that, “The Applicant has provided sufficient information to assure identity, strength, and purity of the drug product” and that “The Applicant has provided sufficient information on raw material controls, manufacturing processes and process controls. Sufficient stability information is provided on the drug product in the NDA to assure strength, purity and quality of the drug product for an expiration dating period of 24 months.” However, the chemistry reviewer recommended that, “From the ONDQA perspective, this NDA is recommended for Complete Response.” The following deficiencies were noted by the chemistry reviewer as precluding approval:

- The Labels and Labeling do not contain sufficient information per 21 CFR 314.125 (b)(6).
- Office of Compliance has issued a “Pending” overall recommendation for all facilities involved and therefore per 21 CFR 314.125 (b) (13) is not acceptable.
- The Applicant has not provided sufficient information to assure quality based on inadequate acceptance criteria for the presence of (b) (4)

In an addendum to the November 2012, the chemistry reviewer concluded in her dated December 21, 2012 review, that, “This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. The Office of Compliance has issued an “ACCEPTABLE” overall recommendation on all the manufacturing facilities. The labels/labeling have adequate information. Therefore, from the ONDQA perspective, this NDA is recommended for APPROVAL.”

The December, 2012 CMC review also stated that a postmarketing commitment (PMC) had been agreed to between the Applicant and an Agency at a teleconference on November 15, 2012 to change the text on the backing film to a darker ink .

The Biopharmaceutics reviewer evaluated the submission and concurred that the Applicant’s proposal to use the approved in-vitro drug release acceptance criteria using previously approved and validated analytical methodologies was acceptable. In his review dated November 16, 2012, he concluded that, “From the Biopharmaceutics view point NDA 202- 211 (000) for Oxytrol for Women (Oxybutynin transdermal system 3.9 mg/day) is recommended for approval.” (See Biopharmaceutics review dated November 16, 2012)

Comment: I concur with the ONDQA and Biopharmaceutics teams that there are no outstanding CMC issues related to this application.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted or requested for this application. After review of the submission, the pharmacology/toxicology reviewer commented in her review dated November 9, 2012 that, “The excipients and impurities/degradants of the drug product have been qualified under NDA21351. There are no new pharmacology/ toxicology issues identified during this review. Based on the previous human use experience of oxybutynin compounds, the agency’s previous review of the nonclinical information on the prescription products, as well as the lack of novel significant toxicity findings during the current review, there is no impediment to approval from a Pharmacology/Toxicology perspective.”

Comment: I concur with the nonclinical review team that there are no outstanding nonclinical issues related to this application.

5. Clinical Pharmacology

No new clinical pharmacology studies were submitted or requested for this application. In his review of the available clinical pharmacology data, the DNCE clinical reviewer concluded that, “There are no proposed changes to the directions for use that required new clinical pharmacology studies to support this Rx-to-OTC switch application.” (See DNCE clinical review dated November 19, 2012).

Comment: I concur with the DNCE clinical reviewer that there are no outstanding clinical pharmacology issues related to this application.

6. Clinical Microbiology

No new clinical microbiology review was submitted or requested for this application of a previously approved and marketed drug product.

7. Efficacy/Statistics

No new clinical trials were submitted or requested for this application. The efficacy of the prescription product, Oxytrol, was cross-referenced to clinical trials originally submitted and reviewed under NDA 21351. Efficacy of Oxytrol was demonstrated in two pivotal double-blind, randomized clinical trials (O99009 and O00011) that enrolled male and female subjects with OAB. The clinical and statistical reviewers concurred that the treatment effect was statistically and clinically meaningful. (See clinical review dated February 21, 2003, and statistical review dated February 13, 2003). At the time of approval, the CDTL review concluded in his summary review dated February 21, 2003, that, “In my opinion, these statistically and clinically significant results (from two adequate and well-controlled Phase 3 trials) demonstrate evidence of efficacy of Oxytrol in the treatment of overactive bladder.”

The DRUP and DNCE clinical reviewers evaluated this OTC application for Oxytrol for Women. In his review dated November 19, 2012, the DNCE clinical reviewer summarized his conclusions regarding efficacy data for Oxytrol for Women and stated that, “For efficacy, the applicant relies on results of trials submitted to support the original NDA for prescription use. See Dr. Gierhart’s and Dr. Batra’s reviews. Assessment of efficacy in controlled clinical trials was based on a decrease in the number of urinary incontinence episodes, frequency of daily micturition, and void volume. Oxybutynin in this transdermal formulation has been shown to be efficacious by these measures.” The DRUP review team concurred with the DNCE review team’s assessment.

Comment: I concur that there are no outstanding efficacy issues related to this application.

8. Safety

The safety database to support use of the prescription Oxytrol was cross-referenced to the clinical trial database originally submitted under NDA 21351. The original clinical trial safety database consisted of a total of 1014 subjects who received at least one dose of Oxytrol. Of these subjects, a total of 522 patients, 258 patients and 74 patients completed 12 weeks, 24 weeks and one year of Oxytrol treatment. The safety profile from this database for the prescription Oxytrol was considered acceptable by the clinical review team. (See CDTL review dated February 21, 2003). Adverse events reported in these clinical trials that were associated with Oxytrol use were almost exclusively related to antimuscarinic effects or to skin irritation. The original clinical reviewer for the Oxytrol safety database concluded that, “The safety profile of the oxybutynin transdermal system is adequate for approval.” (See clinical review dated February 21, 2003).

The postmarketing safety database to support the Oxytrol for Women switch is derived from estimated sales that include nearly (b) (4) patches sold in the US and (b) (4) patches worldwide. Both DRUP and DNCE clinical reviewers evaluated the postmarketing safety database for Oxytrol through a total of 26 periodic safety reports (PSURs) that have been submitted to the NDA.

The DRUP review team evaluated both the preapproval and postmarketing safety databases for the prescription Oxytrol product. The focus of the DRUP review was on the summary of adverse events contained in periodic adverse event reports that had been submitted to the Agency. In his review dated December 17, 2012, the DRUP clinical reviewer stated that, “The adverse events reported during the post marketing period are similar and consistent with those reported during the phase 3 trials.” The DRUP clinical reviewer also evaluated a summary of safety information that had been submitted to the European Regulatory Agency and information on a prescription transdermal oxybutynin gel (Gelnique). The DRUP clinical reviewer summarized his findings of the postmarket experience for Oxytrol as follows, “The leading adverse events reported in this additional safety information are site administration reactions from the transdermal patch and anticholinergic side effects such as dry mouth, blurred vision, constipation, dizziness and

somnolence. These data sources do not identify any significant safety issues beyond those that are seen in the US PADER analysis.”

The DNCE clinical reviewer also evaluated safety data from a completed phase 4 trial (MATRIX – Multicenter Assessment of Transdermal Therapy in Overactive Bladder with Oxybutynin) and safety data obtained from the AERS database, the WHO Database, the AAPCC Database and limited safety data collected from the actual use study (CONTROL). After evaluation of these databases, the DNCE reviewer worked with the DRUP review team and summarized in his November 19, 2012 review, several safety topics of special interest because these conditions could share urinary symptomatology with Overactive Bladder. These conditions included diabetes mellitus, urinary tract infections, undiagnosed pregnancy and bladder cancer. Consumers who have these conditions could potentially use the Oxytrol for Women product, but are unlikely to benefit from use of the oxybutynin product. After review of the adverse events resulting from these conditions in women using oxybutynin, the DNCE and DRUP reviewers concluded that it was unlikely to result in clinically important delays in diagnosis of urinary tract infection, diabetes mellitus, undiagnosed pregnancy. Regarding undiagnosed bladder cancer, the DRUP reviewer commented in his December 2012, review that, “With anticholinergic treatment, it is unlikely that a patient will have a significant improvement in their irritable voiding symptoms. It is reasonable to estimate that the delay in diagnosis caused by inappropriate treatment with Oxytrol for Women would, in the large majority of cases, be short.”

Comment: I also concur with the DNCE and DRUP review teams that although it is difficult to quantify the impact of a delay in diagnosis, it is unlikely that patients with these conditions will see significant improvement and the delay from a trial of Oxytrol use will likely be very limited.

Additional safety signals identified with Oxytrol by the DNCE review team included skin reactions, anticholinergic-specific adverse events (such as dry mouth and constipation), acute urinary retention, narrow angle glaucoma and CNS effects. These identified safety signals are all known side effects of antimuscarinic therapy.

After review of the postmarketing experience, the DNCE clinical reviewer concluded in his review dated November 19, 2012, that, “Based on review of the full complement of postmarketing safety data, this reviewer believes that the data do not suggest that there are any safety signals which would preclude approval for OTC marketing. It seems that any precautions or potential risks associated with use of Oxytrol for Women® can be properly labeled (see Section 9.2 Labeling Recommendations). Whether consumers respond to such warnings appropriately, guiding proper use of the product, is addressed in my review of the CONTROL trial elsewhere.”

The DNCE CDTL also evaluated the safety database, focusing primarily on the available postmarketing data from the available databases and the actual use study. In her review dated December 5, 2012, regarding safety data from the actual use study, she noted that, “...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.” In summary, she concluded that, “the clinical trial data and postmarketing experience support that the oxybutynin TDS (transdermal system) has a relatively benign safety profile.”

Comment: I concur with the DNCE clinical reviewer, DRUP clinical reviewer, and CDTL that there are no outstanding safety issues related to this application. I agree with the CDTL that there are concerns about CNS effects, such as somnolence, with Oxytrol use. However, in my opinion, the revisions that are being proposed by DNCE and addition of a consumer information leaflet makes the risk/benefit acceptable for women who choose to use Oxytrol for Women in the OTC setting.

9. Advisory Committee Meeting

A meeting of the Nonprescription Drugs Advisory Committee (NDAC) was held on November 9, 2012, to discuss the Oxytrol partial OTC switch application (Oxytrol for Women). 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?

Two of the six “no” votes hinged on two concerns. 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. A third concern raised during the November 2012 AC was regarding the possibility of missing bladder cancer or bladder cancer in situ as no medical workup will be performed prior to OTC use.

DNCE considered these key concerns as well as other issues identified during the AC and subsequently held meetings to discuss comments and recommendations from the AC members with DRUP. After evaluation, the DNCE and DRUP review teams concluded that: 1) revised labeling with a consumer information leaflet could communicate both the CNS effects of Oxytrol, and 2) could provide additional information on behavioral techniques for managing OAB. DNCE also considered the issue of use of Oxytrol in patients with undiagnosed bladder cancer or bladder cancer in situ. The DNCE reviewer noted that symptoms relatable to bladder cancer appear to differ significantly enough from overactive bladder. In addition, bladder cancer largely presents with macroscopic hematuria that would assist patients in identifying this as a cancer and distinct from the condition of overactive bladder. These determinations supported DNCE’s reviewer’s conclusion that Oxytrol use, “...would significantly increase the risk of delay of bladder cancer diagnosis.” (See DNCE review dated November 19, 2012)

Comment: I concur with the recommendations of the DNCE and DRUP review teams that the concerns raised at the November 2012 Advisory Committee meeting can be addressed in product labeling.

10. Pediatrics

The submission did not trigger the Pediatric Research and Equity Act and therefore, no input from pediatrics was necessary for this application.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI):

A total of 26 pharmacies from ten communities in the US were used as participating sites to enroll subjects in the pivotal actual use study (CONTROL). From this clinical study, three pharmacy sites and the CRO [REDACTED] (b)(4) were inspected by OSI in support of the Oxytrol application. The OSI reviewer concluded in her clinical inspection summary that, “The data from the sites and the CRO submitted in support of NDA 202211 may be considered reliable in support of the NDA. (See clinical review dated November 2, 2012).

Comment: I concur that there are no outstanding issues related to the clinical sites for this submission.

Division of Medication Error Prevention and Analysis (DMEPA):

DMEPA reviewed the container label, carton and insert label for Oxytrol for Women on November 13, 2012. Their recommendations were reviewed and the agreed to recommendations were implemented including requesting that the Applicant use a darker ink on the text on the backing film. This request was outlined in a postmarketing commitment that was agreed to by the Agency and the Applicant on November 15, 2012.

DMEPA also assessed the proposed tradename “Oxytrol for Women” on June 21, 2012 and again on December 11, 2012, and found it acceptable.

Financial Disclosures:

Financial Disclosure certificates were reviewed by the DNCE clinical reviewer. He determined that, “There do not appear to be any financial relationships between the applicant and the study sites or CRO that would impact the conduct or results of the clinical trials submitted with this application to support approval.” (See DNCE clinical review dated November 19, 2012).

Comment: Based on the conclusions of the DNCE clinical reviewer, there are no outstanding issues related to financial disclosures for this Oxytrol application.

12. Labeling

The primary focus of this submission was DNCE’s review of consumer behavior studies in order to develop acceptable OTC labeling. Development of this partial Rx-to-OTC

switch initially focused on label comprehension and self-selection studies. This NDA submission contained five label comprehension studies and three self-selection studies conducted between 2008 and 2011.

The Social Science reviewer evaluated the findings of these studies in the overall population and the low literate population. The Social Science reviewer noted in her review dated November 15, 2012, that in the pivotal label comprehension study (Study #10053) most warnings and specific OAB symptom identification were in the 80-90% range among the general population and older respondents did not have significantly less comprehension than younger respondents but gaps were noted in other areas such as pregnancy and urinary tract infection. The Social Scientist summarized her findings from these submitted label comprehension and self selection studies and provided recommendations for the proposed OTC label based on these research findings from these studies (See Social Science review dated November 15, 2012).

After completing the label comprehension and self-selection studies, the Applicant completed an actual use study (CONTROL: Protocol #CL2008-13). The actual use study (CONTROL) included a total of 1069 subjects and 785 users with at least one application of Oxytrol. The DNCE statistical reviewer evaluated both the pivotal label comprehension study (#10053) and the actual use study (Protocol #CL2008-13). The one concerning finding from the DNCE statistical review in the actual use study was that, of the 1069 subjects who made an Oxytrol purchase decision, 839 subjects (78.5%) who made a positive purchase decision had ineligibilities according to the label. In his November 16, 2012, review, the DNCE statistical reviewer summarized his findings as follows, “The statistical reviewer does not identify any statistical issues that may preclude the approval of this NDA. However, as the clinical implication of such high label ineligibility rate (78.5%) is beyond the scope of statistical evaluation, the statistical reviewer defers the decision of approval of this NDA to the clinical review team.”

The DNCE clinical review and DNCE CDTL evaluated the findings and comments from the Social Science and DNCE Statistical review team. In his November 2012 review, the DNCE clinical reviewer addressed the concerns raised from findings in the CONTROL trial that were identified by the DNCE statistical reviewer and stated that, “Subjects with many ineligibilities were allowed to purchase and use the drug because the clinical consequences of use may not be significant (stress incontinence, weight loss, use of diuretics) and the applicant wanted to evaluate how the label might be understood and acted upon in a “real world” setting.” In fact, it did not appear that safety issues arose as a result of the inclusion of subjects with one or more label ineligibilities. After review of the issues raised, primarily regarding the CONTROL trial findings, he concluded that, “The applicant met the a priori misuse threshold for the CONTROL trial, supporting proper use.” In summary, he concluded in his November, 2012, clinical review that, “Based on my review of the available data from the clinical perspective, I recommend approval, contingent on the applicant accepting labeling recommendations to support safe and proper use of Oxytrol for Women in the OTC setting.” In her December 2012, review, the CDTL concurred with the DNCE clinical reviewer and recommended

approval of the application contingent on final agreement on labeling as well as resolution of outstanding CMC issues.

Labeling discussions for Oxytrol for Women are in final negotiation. The DNCE review team is working with the DRUP review team, the ONDQA review team and the DMEPA review team to finalize the label, consumer information leaflet, carton and immediate container.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the DNCE Cross-Discipline Team Leader, DNCE clinical reviewer and other review teams that the Oxytrol for Women application should receive an Approval action.

Risk Benefit Assessment:

The oxybutynin transdermal system (tradename Oxytrol) was approved for use in the US since 2003 (NDA 21351). Review of this submission to allow a partial switch of the Oxytrol patch for use in women only for treatment of overactive bladder did not raise any new efficacy or safety concerns for the prescription drug product. In addition, no new safety concerns were identified from the post-marketing data that precluded approval of Oxytrol switching to OTC status other than those previously identified. The tradename for the OTC transdermal system will be “Oxytrol for Women”.

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 such as urinary tract infections and bladder cancers. I concur with the DNCE and DRUP review teams that it is unlikely that use of Oxytrol will result in a clinically significant delay in seeking medical treatment, but more likely that these patients will seek medical advice sooner when these products do not result in clinical improvement. Recommendations from the November 2012 Advisory Committee members were taken into account by the DNCE review team during further labeling revisions for the Oxytrol for Women product.

Labeling comprehension and self-selection studies were reviewed and determined to be acceptable to the DNCE review teams. The DNCE reviewer and CDTL concluded that the patient focused labeling, self-selection and actual use studies support that women who will use Oxytrol for Women are able to make a risk-benefit decision related to use of this product. The DNCE reviewer concluded in his November 19, 2012, review that, “Based on my review of the available data from the clinical perspective, I recommend approval contingent on the applicant accepting labeling recommendations to support safe and proper use of Oxytrol for Women® in the OTC setting. In her review dated December 5, 2012, the DNCE CDTL for this application recommended approval, contingent on: 1) Final agreement on labeling, 2) Satisfactory final inspection reports for the manufacturing and testing sites and 3) Satisfactory resolution of proposal for acceptance criteria for the

presence of (b) (4) All of these outstanding issues were either addressed or will be addressed when final agreement is reached on labeling.

After review of the benefits and risks associated with Oxytrol from preapproval and postmarketing experience with supporting information from label comprehension, self-selection and actual use studies, this recommendation is also supported by the DRUP review teams risk/benefit assessment in their review dated December 17, 2012, that, “Based on the pre-approval and the post-approval data this reviewer has found no evidence that would change the Division’s prior conclusion that Oxytrol is a safe and effective treatment for overactive bladder.” I concur with the review teams that there are no outstanding efficacy or safety issues that preclude approval of this partial switch for Oxytrol for Women.

Therefore, in my opinion, the risk/benefit assessment favors approval of the partial switch for Oxytrol for Women (oxybutynin transdermal system) for treatment of overactive bladder in women in an OTC setting.

Post-Marketing Requirement/Commitments:

- The review teams also determined that no new postmarketing requirements are necessary for this previously approved product.
- As previously stated, a postmarketing commitment between the Applicant and the Agency was agreed to that will change the text on the backing film to a darker ink within one year from the Approval date for this product. The agreed to PMC and timeframe for completion was acceptable to both DMEPA’s and ONDQA’s review teams as well as the Applicant.

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

/s/

AUDREY L GASSMAN
01/02/2013

CLINICAL REVIEW

Application Type 505(b)(1)
Application Number(s) 202-211
Priority or Standard Standard

Submit Date(s) March 26, 2012
Received Date(s) March 26, 2012
PDUFA Goal Date January 25, 2013
Division / Office DRUP/ODE III

Joint Review DNCE/ODE III
Reviewer Name(s) Donald McNellis, M.D.
Review Completion Date 12/17/2012

Established Name Oxybutynin Transdermal System
(Proposed) Trade Name Oxytrol for Women
Therapeutic Class Anticholinergic
Applicant Merck Consumer Care, Inc.

Formulation(s) Transdermal System 3.9 mg/day
Dosing Regimen Apply one patch every (b) (4) 4 days
Indication(s) Treatment of the symptoms of overactive bladder
Intended Population(s) Adult women

Template Version: March 6, 2009

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1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this clinical reviewer, Oxytrol Transdermal System 3.9 mg/day is safe and effective for the treatment of symptoms of overactive bladder (OAB). This opinion is based upon previous reviews of NDA 21-351 in 2003 and subsequent postmarketing monitoring of adverse events.

With respect to switching the product from a prescription to an over-the-counter status, I concur with the Applicant's decision to market Oxytrol for Women only to female patients. The overlap between symptoms of overactive bladder and those of prostate disease would, in my opinion, be difficult for men to evaluate without the assistance of a medical professional.

I believe that a regulatory decision to change the product from a prescription to a non prescription status hinges upon the demonstration of the ability of consumers to appropriately self-diagnose OAB and to use the product in conformance with the over the counter labeling. We defer a recommendation on the approval of this product until the issues of 1) the ability of a patient to self-diagnose the condition and 2) the ability of the label to guide the patient in the safe use of the product have been judged to be adequate by the Division of Nonprescription Clinical Evaluation.

1.2 Risk Benefit Assessment

Oxytrol Transdermal System 3.9 mg/day (Oxytrol) has been previously shown to be a safe and effective prescription treatment for the symptoms of overactive bladder. It was approved for this indication under NDA 21-351 on February 26, 2003. Subsequent postmarketing experience has not significantly altered the safety profile of the drug from a clinical perspective. The Agency continues to consider it a safe and effective treatment for overactive bladder symptoms when used under the direction of a physician.

The benefit of the product is the relief of the symptoms of overactive bladder. NDA 21-351 established that the product was able to significantly improve the symptoms of urinary incontinence and urinary frequency. Improvement of these symptoms is a clinical benefit to patients.

The risks of the product consist primarily of skin irritation by the delivery system and anticholinergic side effects. The most frequent reported side effects are dry mouth, constipation and dizziness. These side effects are generally mild in intensity.

In the non-prescription setting several additional risks must be considered. The risk of incorrect self diagnosis with resulting delay in the diagnosis of a condition with similar

presenting symptoms, such as diabetes, bladder cancer, urinary tract infection or pregnancy, must be considered. This risk is discussed in Section 7.4 of this review.

Also, the risk of a patient using the product in an inappropriate manner must be considered. Labeling must be sufficient so that selection by the correct patient population (i.e. women with overactive bladder) occurs. Labeling must also be sufficient to prevent patients from using the product for inappropriate conditions, in the presence of contraindications or when it has been shown by a reasonable period of use to be ineffective in improving their condition.

The risk benefit assessment in the non prescription setting will be most heavily influenced by a demonstration of the adequacy of the consumer label to reasonably reduce these risks. The Division of Reproductive and Urologic Products is not able to conclude that the risk benefit balance is favorable until the label has been judged by the Division of Nonprescription Clinical Evaluation to be adequate in limiting these risks.

2. Introduction and Regulatory Background

2.1 Product Information

Oxybutynin transdermal system was approved for marketing under NDA 21-351, Trade Name Oxytrol, on February 26, 2003. The Sponsor of that application was Watson Laboratories. The NDA which is the subject of this review represents a request by Merck Consumer Care, who has obtained the over-the-counter rights to Oxytrol from Watson Labs, to change the product from a prescription to an over-the-counter status. The requested switch is a partial conversion to over-the-counter status because the Applicant has requested this change only for women. Oxytrol would remain a prescription product for men.

The oxybutynin transdermal system, Oxytrol, is a three layer matrix design that consists of a translucent backing film, an adhesive matrix, and an overlapped-tab release liner that is removed prior to system application. Individual systems are packed in heat sealed pouches. The nominal active ingredient is oxybutynin. The oxybutynin content of each system is 36 mg. The transdermal dosing regimen is a four day wear period over which the delivery will be approximately 3.9 mg/day. The adhesive matrix contains oxybutynin and triacetin that are dissolved in an (b) (4). The adhesive comprises (b) (4) of the dried adhesive/oxybutynin/triacetin matrix and triacetin approximately (b) (4).

2.2 Tables of Currently Available Treatments for Proposed Indications

The following products are currently available for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. All are prescription

products and are available for use by both men and women. There are currently no approved non-prescription products for the applicant's proposed indication "Treatment of Overactive Bladder."

Table 1. Available Treatments for Symptoms of Overactive Bladder

Active Ingredient	Trade Name	Dose/Formulation	NDA/ANDA	Sponsor	Approval Date
ANTICHOLINERGIC DRUG PRODUCTS					
Oxybutynin	Ditropan XL	Extended Release Tablet, 5mg, 10mg, 15mg	20,897	Janssen Pharms	December 16, 1998
	Oxytrol	Transdermal Patch, 3.9 mg/day	21,351	Watson Labs	February 26, 2003
	Gelnique	Transdermal Gel 10%, 100mg Packets	22,204	Watson Labs	January 27, 2009
	Anturol	Transdermal Gel 3%, Metered Dose Pump	202,513	Arrow Intl	December 7, 2011
	-----	Oral Tablet 5mg	ANDA 71,655	Pliva	November 14, 1988
	-----	Oral Tablet 5mg	ANDA 74,625	USL Pharma	July 31, 1996
	-----	Oral Tablet 5mg	ANDA 75,079	Vintage Pharms	October 31, 1997
	-----	Extended Release Tablet Multiple Strengths	ANDA 76,644	Mylan Pharms	November 9, 2006
	-----	Extended Release Tablet Multiple Strengths	ANDA 76,745	Impax Pharms	November 9, 2006
	-----	Extended Release Tablet Multiple Strengths	ANDA 78,503	Osmotica Pharm	February 4, 2009
	-----	Oral Syrup 5mg/5ml	ANDA 74,520	Silarx	March 29, 1996
	-----	Oral Syrup 5mg/5ml	ANDA 74,868	Wockhardt	February 12, 1997
	-----	Oral Syrup 5mg/5ml	ANDA 74,997	Novex	October 15, 1997
	-----	Oral Syrup 5mg/5ml	ANDA 75,039	Mikart	January 29, 1999
-----	Oral Syrup 5mg/5ml	ANDA	Pharm	December	

Active Ingredient	Trade Name	Dose/Formulation	NDA/ANDA	Sponsor	Approval Date
			75,137	Assoc	18, 1998
	-----	Oral Syrup 5mg/5ml	ANDA 76,682	Vintage Pharms	December 28, 2004
Solifenacin	Vesicare	Oral Tablet 5mg, 10mg	NDA 21,518	Astellas	November 19, 2004
Darifenacin	Enablex	Extended Release Tablet 7.5mg, 15mg	NDA 21,513	Warner Chilcott	December 22, 2004
Fesoterodine	Toviaz	Extended Release Tablet 4 mg, 8mg	NDA 22,030	Pfizer	October 31, 2008
Tolterodine	Detrol	Oral Tablet 1mg	NDA 20,771	Pharmacia	March 25, 1998
	Detrol LA	Extended Release Tablet 2mg, 4mg	NDA 21,228	Pharmacia	December 22, 2000
Trospium	Sanctura	Oral Tablet 20mg	NDA 21,595	Allergan	May 28, 2004
	Sanctura XR	Extended Release Capsule 60mg	NDA 22,103	Allergan	August 3, 2007
	-----	Oral Tablet 20mg	ANDA 91,513	Apotex	December 6, 2011
	-----	Oral Tablet 20mg	ANDA 91,575	Glenmark Generics	August 13, 2010
BETA 3 AGONIST DRUG PRODUCT					
Mirabegron	Myrbetriq	Extended Release Tablet 25mg	NDA 202,611	Astellas	June 29, 2012

2.3 Availability of Proposed Active Ingredient in the United States

Oxybutynin is available by prescription as a treatment for the symptoms of overactive bladder in the formulations shown in **Table 1**. There are no other transdermal system (patch) formulations of oxybutynin available other than Oxytrol. Two transdermal gel products, Gelnique and Anturol, are available.

2.4 Important Safety Issues with Consideration to Related Drugs

All anticholinergic drugs are accompanied by side effects that are manifestations of their mechanism of action. These effects include dry mouth, constipation, change in accommodation, and blurred vision. Urinary and gastric retention has been reported with this class of drugs secondary to the anticholinergic effect on the bladder or gastric musculature, although these reports are relatively uncommon. Similarly, these drugs can worsen narrow angle glaucoma by their effect on the iris.

Angioedema requiring hospitalization and emergency medical treatment has occurred with the first or subsequent doses of oral oxybutynin.

2.5 Summary of Presubmission Regulatory Activity

The original NDA submission (21-351) for Oxytrol transdermal system was submitted on April 26, 2001. This submission sought approval (b) (4) 3.9 mg/day and was supported by the results of one phase 3 study, study O99009. On March 26, 2002 the Sponsor of the NDA received a not approvable letter. The four specific deficiencies in this letter were:

1. The results of the single Phase 3 clinical trial O99009 showed marginal efficacy in the treatment of patients with overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. A statistically significant difference in the number of episodes of incontinence (the primary endpoint) was demonstrated following treatment with the 3.9mg per day dose of Oxytrol versus placebo. This result, however, was not supported by a second confirmatory study and was not considered compelling. Treatment with the Oxytrol 3.9mg per day dose did not demonstrate efficacy for reduction in urinary frequency, a secondary endpoint in Study O99009. We consider demonstration of efficacy for this parameter clinically important for establishing efficacy in the treatment of patients with overactive bladder.
2. Treatment with the (b) (4) per day dose of Oxytrol did not show a statistically significant result when compared to placebo for either urinary incontinence or urinary frequency.
3. Errors involving the transcription of 35 source document diaries call into question results presented on both doses for the primary and secondary efficacy parameters. Results of a reanalysis of the data following correction of these transcription errors have not been presented to the Agency.
4. There was insufficient safety data collected on skin tolerability for the 39cm oxybutynin transdermal system.

In response to this letter the Sponsor took the following actions.

1. (b) (4)
2. They reanalyzed Study O099009, with the reanalysis including all missing diary data and removing all data related to Study Site #12. This was done as recommended by the Division of Scientific Investigations because of irregularities in the data obtained from this site.
3. They conducted a second phase 3 study, number O00011, evaluating the efficacy of the 3.9 mg/day dose over 12 weeks in patients who had previously benefited from anticholinergic therapy.

4. They conducted two additional studies evaluating the cumulative skin irritation resulting from use of the 3.9 mg/day patch.

The Sponsor submitted a Complete Response to the non approvable letter on August 29, 2002. This response included the reanalysis of study O099009, the data for the new efficacy study O00011, and the skin irritation data. Upon review of this data, the Agency concluded that study O099009 demonstrated significantly greater improvement in both number of weekly incontinence episodes and micturition episodes as compared to placebo. They also concluded that the newly submitted study O00011 demonstrated significant improvement in incontinence episodes as compared to placebo, but did not show significant improvement in micturition frequency as compared to placebo. The skin irritation studies were found to show acceptable skin safety.

Based on this submission, NDA 21-351 for the 3.9 mg/day dose of Oxytrol was approved for the treatment of symptoms of overactive bladder on February 28, 2003.

On April 16, 2007 a meeting attended by representatives of the Sponsor, the Division of Nonprescription Clinical Evaluation (DNCE) and the Division of Reproductive and Urologic Products (DRUP) was held. The purpose of the meeting was to discuss the Sponsor's proposed drug development plan to support the switch from prescription to over-the-counter (OTC) marketing. At this meeting the Agency representatives stressed that, although many consumers experience "idiopathic" OAB, the symptom complex is also associated with a myriad of medical conditions. Some of these medical conditions with similar symptoms are clinically serious. The Agency representatives stated that the Sponsor needed to convincingly show that OAB is an appropriate OTC indication by demonstrating the OTC population can distinguish idiopathic OAB from other medical conditions that require the intervention of a qualified intermediary. They also stressed that the Sponsor would need to define an appropriate target OTC population for use of the product given its risk-benefit profile.

At this meeting, the Sponsor's proposed design for a label comprehension study, self-selection study and an actual use study were discussed. FDA provided comments on their perception of the deficiencies of the protocols proposed by the Sponsor and the potential label was extensively discussed.

The Division of Nonprescription Clinical Evaluation (DNCE) provided further guidance to the Sponsor for their label and the proposed label comprehension study in a letter dated October 3, 2007. In this letter, DNCE again emphasized the importance of assuring adequate self-selection. The letter stated:

"We are concerned that irritative voiding symptoms may improve with anticholinergic therapy even if the symptoms are due to significant pathology. This could potentially delay diagnosis of a significant medical condition. Additionally, if the purpose of the statement telling consumers to have regular physical exams is to ensure that

consumers see a physician, this is counter to what a nonprescription product is, one that can be used safely and effectively without the intervention of a healthcare provider.”

An end-of-phase 2 meeting was held on October 13, 2009. The minutes of this meeting indicate that the FDA remained concerned about the self-selection issue. The minutes stated:

“We recommend that you consider including a urine dipstick in the Oxytrol package that measures glucose, white blood cells, and blood in order to enable consumers who may have undiagnosed diabetes, urinary tract infections, and hematuria to obtain the information needed to correctly select not to use Oxytrol.”

The FDA also stated at the meeting that the urine dipstick advice was a suggestion as a path forward, not a requirement. The proposed label comprehension and self-selection studies were discussed and the FDA provided comments on the issues of potential undiagnosed pregnancy, undiagnosed diabetes, undiagnosed UTI, and undiagnosed bladder cancer. At this point in development the Sponsor had decided to target the product to adult women only, and the issue of labeling for prevention of purchase of the product by men was discussed. The Sponsor’s rationale for targeting women was that the overlap in the symptoms of overactive bladder and those caused by prostate disease would make self selection difficult for men. The FDA also stated the importance of the labeling adequately communicating the message that patients should stop drug use and seek medical help if their symptoms fail to improve or worsen.

A pre-NDA meeting was held on September 12, 2011. At this meeting, discussion centered on analyses to be provided in the NDA submission, the content of the Integrated Summary of Efficacy and Integrated Summary of Safety, the post-marketing data to be included and the format of the NDA submission.

3. Significant Efficacy/Safety Issues Related to Other Review Disciplines

3.1 Division of Nonprescription Clinical Evaluation

The Division of Nonprescription Clinical Evaluation (DNCE) is evaluating the information submitted by the Sponsor to support the switch of Oxytrol from a prescription to an over-the-counter product for women. These studies include the ability of a consumer to reliably self-diagnose the condition of overactive bladder, to adequately comprehend the product label, and to use the product in a manner consistent with the label.

It is the Division of Reproductive and Urologic Products’ (DRUP’s) opinion that these studies should convincingly demonstrate that consumers can reliably diagnose the condition, self select, and use the product in a safe manner. This demonstration is an essential factor in making an approval decision regarding this switch.

4. Sources of Clinical Data

4.1 Tables of Studies/Clinical Trials

During the review of NDA 21-351 the efficacy of Oxybutynin Transdermal System (TDS) was previously established based on the results of two clinical trials: These are shown in **Table 2**.

Table 2. Phase 3 Trials Submitted with NDA 21,351

Trial Number	Design & Control Type	Treatment Duration	Arms	N	Primary Endpoint
O99009	Randomized, double-blind, parallel	12 Weeks	Placebo 13, 26 and 39 cm ² Patch	520	Change in the number of episodes Of incontinence per week
O00011	Randomized, double-blind, parallel	12 Weeks	Placebo, Tolterodine 4mg, Oxybutynin TDS 3.9 mg/day	361	Change in mean urinary incontinence Episodes during Treatment period

Source: NDA 202,211, Module 2.7.3, Table 1, page 7.

The Sponsor has conducted no additional evaluations of efficacy since the original approval in 2003.

4.2 Review Strategy

The two efficacy studies were reviewed as part of the approval process for original NDA 21-351 in 2003. The clinical and statistical reviews¹ established that these two studies did provide sufficient evidence of efficacy for the indication of treatment of the symptoms of overactive bladder including urinary frequency, urgency and urge incontinence.

4.3 Discussion of Individual Studies/Clinical Trials

Study O99099

This study consisted of three periods for a total study duration of 1 year: (1) a 12-week, double-blind, placebo-controlled period evaluating three doses of Oxybutynin TDS, followed by (2) a 12-week, open-label, dose-titration safety period, and (3) a subsequent 28-week, fixed-dose, open-label safety extension.

The double-blind period was a multi-center, randomized study in male and female patients with OAB who exhibited symptoms of urge incontinence and urinary frequency.

¹ NDA 21,351. Medical Officer Clinical Review. Ashok Batra, M.D. February 7, 2003. and Statistical Review and Evaluation, Sue-Jane Wang Ph.D. February 13, 2003.

The primary objective of the double-blind period of the study was to compare the safety and efficacy of three doses of Oxybutynin TDS with placebo during 12 weeks of treatment. The secondary efficacy objectives of the double-blind period included comparisons of daily urinary frequency, urinary volume per void, quality of life (QoL) scores, Global Assessment of Disease State, and safety assessments. In addition, plasma concentrations of oxybutynin and its primary active metabolite, N-desethyloxybutynin (N-DEO), were measured to evaluate population pharmacokinetics.

This study consisted of a screening period of 3 to 4 weeks followed by a 12-week, randomized, double-blind, placebo-controlled treatment period. Patients who met the eligibility criteria during the screening and baseline evaluations were randomized to one of the following treatment groups: 13 cm², 26 cm², or 39 cm² Oxybutynin TDS, or placebo TDS. The active patch delivered a nominal dose of 0.1 mg oxybutynin/cm² surface area per day. Hence, the 13, 26 and 39 cm² patches delivered nominal daily doses of 1.3, 2.6, and 3.9 mg oxybutynin, respectively.

Patients who completed the double-blind period were then eligible to enter the 12-week, open label, dose-titration safety period. The objectives of the 12-week open-label safety period included characterization of the distribution of doses used by the patients in the study, confirmation of continued efficacy using both objective and subjective measures, and continued treatment safety in approximately 300 patients. Changes in QoL scores over the 12-week open-label safety period were also evaluated, and plasma concentrations of oxybutynin and N-DEO were measured. In the open-label safety period, all patients began treatment with a single 1.3 mg/day Oxybutynin TDS applied twice weekly. The dose of medication was titrated by the investigator after 2 and 4 weeks of treatment based on the patient's symptoms and remained fixed for the last 8 weeks. Patients who completed the 12-week open-label safety period had the option to continue into a 28-week, open-label, fixed-dose safety extension.

A total of 520 patients were enrolled into the study of which 447 completed the double blind phase. Four hundred eleven subjects enrolled in the 12-week open-label phase, and 142 entered the subsequent 28-week extension.

Study O00011

This was a multicenter double blind, 3-arm study comparing the safety and efficacy of Oxytrol 3.9 mg/day with tolterodine oral treatment and placebo in male and female patients who had previously achieved a beneficial response from pharmacological treatment of their OAB symptoms. The primary efficacy endpoint was the change in average number of urinary incontinence episodes per day from baseline to end of treatment as recorded on a 3-day urinary diary. Secondary objectives included change from baseline for urinary frequency, urinary void volume, patient QoL scores, and Global Assessment of Disease State.

The study included a screening period of 3 to 4 weeks followed by a 12-week treatment period. Screening consisted of a 2-week washout from current overactive bladder treatment, practice of bladder and fluid management techniques, and completion of a 3-day urinary diary at the end of the 2-week period. Patients who met the eligibility criteria then received one of three randomized treatments: 3.9 mg/day Oxybutynin TDS plus placebo capsules, 4 mg tolterodine long-acting capsules plus placebo TDS, or placebo treatment (capsules and TDS). Transdermal systems were applied twice weekly (approximately every 3.5 days) to the abdomen and capsules taken orally once daily throughout the 12-week treatment period.

A total of 361 patients were enrolled in the study, of which 320 completed the study. At the end of the main study, 284 patients entered a 12-month open-label extension study and were treated with twice weekly Oxytrol.

5. Review of Efficacy

Efficacy Summary

Two adequate and well-controlled Phase 3 trials were conducted in men and women that provided evidence that shows that the oxybutynin TDS 3.9 mg/day product provides a modest improvement over placebo in treating the symptoms of overactive bladder. This difference was statistically significant and is clinically meaningful.

5.1 Indication

The treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

5.1.1 Methods

The designs of studies O99099 (Study 09) and O00011 (Study 11) are presented in Section 4.3 Discussion of Individual Studies/Clinical Trials.

5.1.2 Demographics

The patients participating in study 09 were primarily elderly Caucasian women with a lengthy history of symptoms of overactive bladder. The overall study population included both men and women of Caucasian, Black, Asian/Pacific Islander, and Hispanic ethnicity. Patient age ranged from 20 to 88 years. The mITT and Evaluable cohorts were comparable in demographic characteristics. Patient demographics in the 12-week open-label safety period were similar to those for the double-blind period and are presented in Table 3.

Table 3. Demographic and Baseline Characteristics – Study 09

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

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

Patients participating in study 11 were primarily elderly Caucasian women, although the study included both men and women of Caucasian, Black, Asian/Pacific Islander and Hispanic ethnicity. The mean age of patients was 63.5 ± 12.6 years. The treatment groups were balanced with respect to other physical characteristics such as height, weight, and BMI; general medical history; urinary history; and current pharmacological treatment for overactive bladder. Concurrent medical history was representative of the medical problems typically occurring in an older population, and was similar between treatment groups. The majority of patients, approximately 55% in all treatment groups, had a history of cardiovascular and/or head/ears/nose/throat disease, about 64% had a history of gastrointestinal disease, and about 84% had a history of musculoskeletal disease.

Table 4. Demographic and Baseline Characteristics – Study 11

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

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

Reviewer's comment: Both studies were heavily weighted with female subjects.

5.1.3 Subject Disposition

Study 09

Seventy major protocol deviations were identified in 66 patients during the double-blind phase of the study. The majority (64, 91.4%) of deviations consisted of a significant lack of compliance with the dosing regimen (31 patients), patients who were entered into the study who did not meet the eligibility criteria (18 patients), and patients who received an excluded concomitant medication (15 patients). With the exception of six patients who received the wrong treatment (for handling of improper randomization), all patients with major deviations were excluded from the Evaluable cohort. All 66 patients with major protocol deviations were included in the mITT cohort.

The 31 patients with significant lack of compliance (i.e., they failed to use at least 50% of the expected number of TDS during any given treatment period) included 4 patients in the placebo group, 7 patients in the 1.3 mg/day group, and 10 patients each in the 2.6 mg/day and 3.9 mg/day groups. One of the 31 patients was discontinued from the double-blind period due to noncompliance with the dosing regimen. Two patients were allowed to continue treatment and had improved compliance by the end of the double-blind period.

Three patient cohorts were used in the analysis of efficacy: the mITT, the mITT omitting Site 12 and Evaluable cohorts. The mITT cohort (515 patients [99.0%]) was defined as all patients who received at least one application of a TDS and provided data for at least

one efficacy assessment after the first application. Because of errors that occurred for 6 patients during treatment randomization of the double-blind period, the treatment assignment used for analysis using the mITT cohort was the treatment actually received. The mITT cohort omitting Site 12 (502 patients) was defined as the subset of the mITT cohort that participated in the study from all sites except Site 12. The Site 12 patients were excluded due to data collection/reporting irregularities identified at the site.

Study 11

Of the 733 screened patients, 361 were enrolled and randomized at 48 sites: 121 (33.5%) to receive 3.9 mg/day Oxybutynin TDS, 117 (32.4%) to receive placebo and 123 (34.1%) to receive 4 mg tolterodine long-acting capsules. The primary reason for not qualifying was failure to meet the required frequency of incontinence episodes (108), followed by patient decision not to participate (90). Three hundred twenty (88.6%) of the 361 patients completed the double-blind period. Of the 41 (11.4%) patients who discontinued early from the study, 23 withdrew due to AE's, 14 due to patient decision to withdraw, 3 due to protocol violations and 1 was lost to follow-up.

Overall compliance was over 90% throughout the study, and was similar for the three treatment groups. Mean compliance for TDS application ranged from 91.4% to 93.2% at endpoint, with an overall compliance of 92.2%. There were no differences in compliance for patients receiving active versus placebo TDS systems. Mean compliance for tolteradine capsule administration ranged from 90.8% to 93.7%. There were no differences in compliance for patients taking active versus placebo capsules. Although nine patients failed to use as least 50% of the expected number of TDS or capsules, no patients were withdrawn from the study due to lack of compliance.

5.1.4 Analysis of Primary Endpoint(s)

Study 09

The primary endpoint was the change from baseline in the number of urinary incontinence episodes per week. The results are shown in Table 5.

Table 5. Results for the primary efficacy endpoint, number of urinary incontinence episodes per week, in Study 09

	Placebo		Oxybutynin TDS					
			1.3 mg/day		2.6 mg/day		3.9 mg/day	
	N=127		N=127		N=128		N=120	
	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD
Baseline								
Mean and SD	37.7	24.0	38.2	26.5	35.8	22.5	34.3	18.2
Median	30.0		31.0		30.0		31.0	
Change from Baseline to Endpoint								
Mean and SD	-19.2	21.4	-18.2	19.7	-16.8	17.9	-21.0	17.1
Median	-15.0		-15.5		-14.0		-19.0	
p-value			0.9927		1.000		0.0265	

Source: NDA 21-351 Clinical Review.

Reviewer's comment: The oxybutynin TDS (3.9 mg/day) resulted in a mean decrease of 19 episodes per week as compared to a decrease of 15 episodes per week for placebo. This difference was statistically significant and was judged by the clinical review team to be a clinically meaningful difference.

Study 11

The primary endpoint was the change from baseline in the number of urinary incontinence episodes per day. The results are shown in Table 6.

Table 6. Results for the primary efficacy endpoint, number of urinary incontinence episodes per day, in Study 011

	Placebo	Tolterodine	Oxytrol
	n = 117	n = 123	n = 121
Number at baseline			
Mean (SD)	5.0 (3.2)	5.0 (2.9)	4.7 (2.9)
Median	4.0	4.0	4.0
Change from Baseline to Endpoint			
Mean (SD)	-2.1 (3.0)	-3.2 (2.8)	-2.9 (3.0)
Median	-2.0	-3.0	-3.0
P-value versus placebo comparing least squares adjusted means		0.0011	0.0137

Source: NDA 21-351 Clinical Review.

Reviewer's comment: Oxytrol resulted in a mean decrease of 3 episodes per day as compared to a decrease of 2 episodes per day for placebo. This difference was statistically significant and was judged by the review team to be a clinically meaningful difference. There was no statistically significant difference between Oxytrol and tolterodine.

5.1.5 Analysis of Secondary Endpoints(s)

Study 09

For study 09 there were two main secondary endpoints – change from baseline in daily urinary frequency and change from baseline in average urinary void volume. The results are shown in the following tables.

Table 7. Results of the secondary efficacy endpoint, daily micturition frequency, in Study 09

	Placebo		Oxybutynin TDS					
	N=127		1.3 mg/day		2.6 mg/day		3.9 mg/day	
	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD
Baseline								
Mean and SD	12.3	3.5	12.5	3.7	11.8	2.8	11.8	3.1
Median	11.0		11.0		11.0		11.0	
Change from Baseline to Endpoint								
Mean and SD	-1.6	3.0	-1.9	2.6	-1.8	2.4	-2.2	2.5
Median	-1.0		-2.0		-2.0		-2.0	
p-value			0.6805		0.3510		0.0313	

Source: NDA 21-351 Clinical Review.

Table 8. Results of the secondary efficacy endpoint, average urinary volume voided per void in milliliters, in Study 09

	Placebo		Oxybutynin TDS					
	N=127		1.3 mg/day		2.6 mg/day		3.9 mg/day	
	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD	Mean/Median	SD
Baseline								
Mean and SD	175.9	69.5	164.8	68.8	155.7	63.0	171.6	65.1
Median	166.5		162.0		145.5		168.0	
Change from Baseline to Endpoint								
Mean and SD	10.5	56.9	8.6	68.0	25.1	58.3	31.6	65.6
Median	5.5		6.0		19.0		26.0	
p-value			0.9432		0.0063		0.0009	

Source: NDA 21-351 Clinical Review.

Reviewer's comment: The 3.9 mg/day TDS resulted in a mean decrease of 2.2 micturitions per day as compared to a decrease of 1.6 micturitions per day for placebo. This was a statistically significant difference. The mean void volume for subjects on the 3.9 mg/day TDS increased by 31.6 cc as compared to an increase of 10.5 cc for subjects receiving placebo. This was also a statistically significant difference.

Study 11

The main secondary endpoints for this study were the same as those for study 09 and are shown in the following tables.

Table 9. Results of the secondary efficacy endpoint, number of micturitions per day, in Study 011

	Placebo n = 117	Tolterodine n = 123	Oxytrol n = 121
Number at baseline (Visit 3)			
Mean (SD)	12.3 (3.3)	12.1 (3.3)	12.4 (2.9)
Median	12.0	12.0	12.0
Change from baseline at endpoint			
Mean (SD)	-1.4 (2.7)	-2.2 (2.6)	-1.9 (2.7)
Median	-1.0	-2.0	-2.0
P-value versus placebo comparing least squares adjusted means		0.0025	0.1010

Source: NDA 21-351 Clinical Review.

Table 10. Results of the secondary efficacy endpoint, average urinary volume voided per void in milliliters, in Study 011

	Placebo n = 117	Tolterodine n = 123	Oxytrol n = 121
Average at baseline (Visit 3)			
Mean (SD)	175.0 (68.0)	165.2 (61.1)	164.8 (62.3)
Median	171.0	150.0	160.0
Change from baseline to endpoint			
Mean (SD)	9.3 (63.1)	29.3 (56.9)	32.0 (55.2)
Median	5.5	29.0	24.0
P-value versus placebo comparing least squares adjusted means		0.0017	0.0010

Source: NDA 21-351 Clinical Review.

Reviewer's comment: The point estimate results for study 11 with respect to change in urinary frequency are very similar to those of study 09. However, the difference in number of micturitions per day did not reach statistical significance in this study. The increase in volume per void was significantly increased with Oxytrol as compared to placebo.

5.1.6 Other Endpoints

Other endpoints were evaluated by the Sponsor, but these are not relevant to the current application.

5.1.7 Subpopulations

No subpopulations were evaluated.

5.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study 09 demonstrated that the Oxybutynin TDS 3.9 mg/day product has efficacy from a statistical and clinical perspective, but the lower dose products were not shown to be effective.

5.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy evaluation was 12 weeks as agreed by the Sponsor and the Division of Reproductive and Urologic Products (DRUP). Long term efficacy evaluation was not studied, but the 12-week duration was considered acceptable from a clinical perspective for a product for this chronic indication.

5.2 Discussion of Onset of Effect

In an over-the-counter setting it is important to provide consumers with information concerning a time period within which they can reasonably expect to see an effect of the product. This is important since the consumer will be self-diagnosing the condition. If the expected effect is not seen they should be advised to consult a physician so that other potential causes of their symptoms can be considered.

For this reason, reviews of studies 09 and 11 were assessed for information concerning the onset of a significant drug effect on the patient's symptoms.

In Study 09 the first on-treatment evaluation of efficacy was done at Week 3 and was based on 7 day voiding diaries. It was found that there was a significant improvement in incontinence with Oxybutynin TDS 3.9 mg/day as compared to placebo at the Week 3 visit and that this effect was maintained throughout all subsequent visits. Similarly, the increase in average void volume with Oxybutynin TDS 3.9 mg/day was significantly greater than the increase seen with placebo beginning at Week 3.

In Study 11 the first on-treatment evaluation of efficacy was done at Week 2 and was based on 3 day voiding diaries. It was noted that the greatest reduction in incontinence episodes occurred during the first 2 weeks of treatment and that this improvement was sustained for the remainder of the treatment period. Void volume increased during the first 2 weeks of treatment, but the maximal increase in void volume was seen at week 6. In this study there was no statistically significant improvement in urinary frequency.

Reviewer's comment: *Based on incontinence it is reasonable to expect that patients will see significant improvement in the first 2 weeks of treatment. It is difficult to state, based on the available information, when patients can reasonably expect to see noticeable improvements in urinary frequency. This reviewer believes that it would be*

prudent to recommend that consumers who do not see improvement in their symptoms within 2 weeks consult their physician for evaluation of those symptoms.

6. Review of Safety

6.1 Methods

The safety of Oxybutynin TDS 3.9 mg/day (Oxytrol) was initially established by the studies submitted to the NDA to support NDA 21351. This review briefly summarizes information provided in the previous submissions.

Oxytrol was approved by the FDA on February 26, 2003 and has been marketed in the US since June 2003. Oxytrol has been marketed outside of the US since August 2004. This review will evaluate the post-marketing safety report information that has been submitted during this period of marketing.

6.2 Review of Safety Based on Studies Submitted to Support NDA 21351

NDA 21-351 supported the FDA approval of Oxytrol as a prescription drug for the symptomatic treatment of OAB and urge urinary incontinence. The NDA submission included a full analysis of safety data from a series of phase 1 trials, a single phase 2, and two phase 3 studies.

This section provides a brief overview and synopsis of the safety data provided with NDA 21-351 which approved prescription use of Oxytrol in 2003. The dose being considered for OTC use, 3.9 mg/day, is identical to the currently approved prescription drug. However, studies submitted with NDA 21351 evaluated a range of doses of oxybutynin (the active drug substance) from 1.3 mg/day to 5.2 mg/day.

6.2.1 Patient Demographics and Exposure

In the original NDA trials, the mean age of the OAB/urinary incontinence patients was 62 years (range 18 – 89 years) and 46% were over age 65. Ninety-one percent of the patients were female and 92% were Caucasian. Exposure ranged from 1.3 mg/day to 5.2 mg/day transdermal delivery patches. The majority of subjects received transdermal oxybutynin at doses of 1.3, 2.6 and 3.9 mg/day. Duration of exposure ranged from 1 – 428 days, with an average of 150.5 days. Table 11 shows the exposure for each study.

Table 11. Exposure to Oxybutynin TDS, Placebo TDS and Oral Oxybutynin – NDA 21351

Population	Study ID	Placebo-controlled Exposures		Active-controlled Exposures		Uncontrolled Exposures
		Placebo TDS	Oxybutynin TDS	Oxybutynin Oral	Oxybutynin TDS	Oxybutynin TDS
Healthy Volunteers	O96003	-	-	16	15	-
	O96005	-	-	17	18	-
	O96006	-	-	-	-	24
	O96007	-	-	-	-	26
	Subtotal	-	-	33	33	50
OAB Patients	O96017	-	-	-	-	-
	O99009-DB	132	388	-	-	-
	O99009-OL	-	-	-	-	411
	O99009-EX	-	-	-	-	142
	O00011-DB	117	121	-	-	-
	Subtotal	249	509	38	38	553
Total	249	509	71	71	603	

Source: Table 7.1-1 of Module 8, Integrated Summary of Safety, NDA 21-351.

O96017 is a phase 2 dose ranging study. Studies O99009 and O00011 are the two phase 3 efficacy studies. DB = double blind, OL = open-label, and EX = extension portions of the phase 3 studies, respectively.

Reviewer's comment: Patient exposure was considered adequate by the review team for the purposes of evaluation of safety of the Oxytrol TDS patch

6.2.2 Incidence of Adverse Events

In the original NDA trials, the overall incidence of Adverse Events (AEs) was greater in the active oxybutynin TDS groups (73.0%) compared to the placebo TDS (56.6%) groups. Treatment-related AEs were also more common in active TDS treated subjects (46.6%) than TDS placebo-treated patients (24.5%) with a trend toward higher incidences of AEs with an increasing dose. Localized skin reactions at TDS application sites, primarily pruritus, were the most common treatment-related adverse events during the studies, occurring in 23.1% of active oxybutynin TDS groups. The incidence of application site AEs in subjects receiving active oxybutynin TDS treatment was approximately twice that observed for patients receiving placebo TDS. The most common systemic AEs were anticholinergic side effects, consistent with the known pharmacology of oxybutynin. Dry mouth was the most common anticholinergic AE, reported by 8.6% of patients receiving oxybutynin TDS in controlled and uncontrolled trials. The incidence of dry mouth, however, was similar for oxybutynin and placebo TDS treatment (7.5% and 5.2% respectively) during controlled trial periods. Application site adverse events decreased with duration of exposure, affecting 11.5% of patients treated from 0-6 weeks, 11.2% treated for 6-12 weeks, 11.2% of patients treated for 12-24 weeks, and 6.3% for patients treated for >24 weeks. The incidence of discontinuation

due to treatment-related AEs reflected this trend, with 6.6%, 4.1%, 5.8%, and 3.5% discontinuations from the four exposure groups, respectively.

Table 12 lists treatment-emergent AEs occurring in at least 2% of subjects during treatment over the 12-week period of the controlled trials. AEs are reported in descending order of frequency, and compares patients receiving oxybutynin TDS (all doses) and placebo TDS, respectively. As shown in Table 12, there were few AEs which were reported by at least 2% of patients in the trial. The most frequently reported AE, application site pruritus, was observed in greater frequency in patients treated with oxybutynin TDS compared to placebo TDS. A similar pattern was observed for application site erythema. The controlled trials also included 38 patients who received oral oxybutynin, however, none of these patients reported pruritus or erythema. Dry mouth was the second-most frequently reported AE but occurred with similar frequency among patients who received either the oxybutynin or placebo TDS. In contrast to transdermal delivery, 22 of the 38 patients (57.9%) who received oral oxybutynin reported dry mouth, and the incidence was significantly greater than the 5.2 – 7.5% reporting dry mouth associated with the placebo TDS.

Table 12. Summary of Adverse Events Seen in >2% of Patients Treated With Oxybutynin TDS and Placebo TDS during 12 Weeks of Treatment

Preferred Term	Oxybutynin TDS (All Doses) N = 547		Placebo TDS N = 249	
Mean Exposure, days	70.5		69.7	
Patient's w/AEs, # (%)	338 (61.8%)		141 (56.6%)	
Preferred Term	Total # AEs	# Treatment-Related AEs ¹	Total # AEs	# Treatment-Related AEs
Application Site Pruritus	74 (13.5%)	73 (13.3%)	13 (5.2%)	13 (5.2%)
Mouth Dry	41 (7.5%)	41 (7.5%)	13 (5.2%)	13 (5.2%)
Application Site Erythema	28 (5.1%)	28 (5.1%)	6 (2.4%)	6 (2.4%)
Diarrhea	25 (4.6%)	14 (2.6%)	14 (5.6%)	5 (2.0%)
Inflicted Injury	21 (3.8%)	0	7 (2.8%)	0
Rhinitis	21 (3.8%)	0	9 (3.6%)	0
Headache	20 (3.7%)	13 (2.4%)	7 (2.8%)	6 (2.4%)
Constipation	19 (3.5%)	17 (3.1%)	7 (2.8%)	5 (2.0%)
Nausea	18 (3.3%)	10 (1.8%)	8 (3.2%)	3 (1.2%)
Urinary Tract Infection	17 (3.1%)	2 (0.4%)	11 (4.4%)	3 (1.2%)
Sinusitis	17 (3.1%)	0	4 (1.6%)	0
Dizziness	15 (2.7%)	10 (1.8%)	6 (2.4%)	3 (1.2%)
Myalgia	15 (2.7%)	6 (1.1%)	2 (0.8%)	1 (0.4%)
Back Pain	15 (2.7%)	4 (0.7%)	8 (3.2%)	1 (0.4%)

Source: Table 8.1.3 of Section 8 of NDA 21-351; Integrated Summary of Safety, Watson Pharmaceuticals, 2002.

1: Related included AEs with possible, probable, or definite relation to test article as determined by the investigator. Studies included O96017, and double-blind treatment periods of O99009 and O00011.

Table 13 provides a summary of treatment-emergent AEs from all phases of the phase 2 and phase 3 trials reported by at least 2% of patients. Only data for oxybutynin TDS are reported. Data are only reported for overall treatment which includes 443, 436, 454,

and 23 patients who received treatment with a 1.3 mg/day, 2.6 mg/day, 3.9 mg/day (approved product) and 5.2 mg/day transdermal patch, respectively. Overall mean duration of exposure was 146.1 days, and represented mean exposures of 50.9, 74.5, 91.0 and 18.8 days to transdermal patches of 1.3 mg/day, 2.6 mg/day, 3.9 mg/day and 5.2 mg/day, respectively. The largest dose patch was only evaluated in the single phase 2 study.

As summarized in Table 13, application site reactions remained the most frequently reported AE through all periods of the phase 2 and phase 3 efficacy studies. With longer use of oxybutynin TDS, a greater incidence of urinary tract infections was observed, likely reflecting the predominantly female patient population who are at greater risk for UTI versus their male counterparts. Although dry mouth was observed, its frequency did not increase over that reported during the controlled periods of these studies. Other AEs reported by at least 2% of the study population included headache, diarrhea, constipation, nausea, rhinitis and sinusitis.

Table 13. Summary of Adverse Events Seen in >2% of Patients Treated With Oxybutynin TDS During Controlled and Open-Label Treatment Phases

Preferred Term	Oxybutynin TDS (All Doses) N = 663	
Mean Exposure, days	146.1	
Patient's w/AEs, # (%)	484 (73.0%)	
Preferred Term	Total # AEs	# Treatment Related AEs ²
Application Site Pruritus	96 (14.5%)	95 (14.3%)
Urinary Tract Infection	67 (10.1%)	8 (1.2%)
Mouth Dry	57 (8.6%)	57 (8.6%)
Inflicted Injury	47 (7.1%)	2 (0.3%)
Diarrhea	44 (6.6%)	21 (3.2%)
Application Site Erythema	38 (5.7%)	38 (5.7%)
Headache	36 (5.4%)	20 (3.0%)
Constipation	30 (4.5%)	26 (3.9%)
Rhinitis	30 (4.5%)	3 (0.5%)
Application Site Reaction	25 (3.8%)	23 (3.5%)
Nausea	25 (3.8%)	14 (2.1%)
Back Pain	25 (3.8%)	5 (0.8%)
Sinusitis	24 (3.6%)	0
Dizziness	23 (3.5%)	15 (2.3%)
Abdominal Pain	20 (3.0%)	8 (1.2%)
Application Site Rash	20 (3.0%)	20 (3.0%)
Upper Respiratory Tract Infection	18 (2.7%)	1 (0.2%)
Vision Abnormal	16 (2.4%)	15 (2.3%)
Influenza-Like Symptoms	14 (2.1%)	0
Dysuria	14 (2.1%)	6 (0.9%)

Source: Table 8.1.4, of Section 8 of NDA 21-351; Integrated Summary of Safety, Watson Pharmaceuticals, 2002.

Reviewer's Comment: *The adverse events seen in the original trials submitted to the NDA are mainly those of skin irritation and anticholinergic side effects. The increased incidence of urinary tract infections seen in the controlled and open label phases is*

unclear, but is likely to be related to the patients underlying voiding problem and is not likely to represent a drug effect.

6.2.3 Discontinuations Due to Adverse Events

Overall, 13.7% of patients discontinued oxybutynin TDS treatment due to adverse events; 11.0% discontinued due to treatment-related AEs. Treatment-related discontinuations, mostly due to application site reactions, were more common in patients receiving active treatment compared to those receiving placebo and discontinuations due to treatment related adverse events tended to increase with increasing oxybutynin TDS dose. Discontinuation rates due to AEs for patients receiving placebo TDS were approximately one third of those in the overall TDS groups in controlled trials (2.8% vs. 9.0%, < 6 weeks of treatment; 3.6% vs. 12.4%, 0-12 weeks of treatment). A larger difference between placebo and active treatment in controlled trials was observed for treatment-related AEs (0.8% vs. 7.5%, controlled studies < 6 weeks; 2.6% vs. 10.4%, controlled studies 0-12 weeks). Dry mouth accounted for a discontinuation rate of only 0.8%. Discontinuation rates tended to decrease with increasing duration of exposure.

No deaths were reported during treatment in any study. Two patients died from nonstudy-related causes: heart attack and malignant mixed Müllerian tumor. One death occurred prior to the patient initiating oxybutynin TDS treatment, and the other, following completion of study participation.

Reviewer's comment: *The drug was reasonably well tolerated in the trials and review of the discontinuations from adverse events revealed an acceptable safety profile for this product.*

6.2.4 Adverse Event Severity

Patients receiving oxybutynin TDS treatment reported a total of 1,867 AEs, the majority of which were mild or moderate in severity. Less than half of the AEs (41.2%) were considered related to drug treatment. Overall, 98 drug-related AEs were graded as severe, of which 64 (65.3%) were application site-related events. In descending order of frequency, these included: severe erythema (23 events), pruritus (18 events), "reaction" (8 events), rash (6 events), vesicle (5 events), and burning, effusion, macules and petechia (1 event each). Only 1 patient reported severe dry mouth while being treated with a 1.3 mg/day oxybutynin TDS (study O99009). In contrast, 8 of 38 patients in the phase 2 study who received oral oxybutynin reported severe dry mouth. Two patients receiving oxybutynin TDS reported severe constipation and 3 patients reported dizziness. The overall incidence rate of severe constipation and dizziness was 0.3% and 0.5%, respectively. The incidence of severe AEs was generally greater in the 3.9 mg/day dose group. For the oxybutynin TDS group, 6.6% of AEs in the 3.9 mg/day

group were severe compared with 3.4% and 3.7% in the lower dose groups (1.3 mg/day and 2.6 mg/day dose groups, respectively).

Reviewer's comment: *The adverse event profile reported was acceptable to the clinical review team.*

6.2.5 Serious Adverse Events

Thirty-seven subjects experienced a total of 47 SAEs in the 19 integrated and nonintegrated trials. None of the SAEs was related to study drug. No SAEs occurred in healthy volunteers in the integrated studies. Most SAEs were of short duration and resolved without sequela prior to discharge from the study. As a result of the SAEs, 9 patients discontinued early. The remaining 28 patients completed the study according to the dosing regimen. Of the 9 patients who discontinued, 2 patients (one each in the 2.6 mg/day and placebo groups) suffered moderate chest pain, 1 patient in the 1.3 mg/day group had a moderate syncope episode, 1 patient in the oxybutynin TDS 1.3 mg/day group had severe episodes of pneumonia/dyspnea as well as severe sepsis, and 1 patient in the 3.9 mg/day group experienced severe pancreatitis in the controlled period of Study O99009. Two patients discontinued from the uncontrolled period of Study O99009, one patient in the 1.3 mg/day group due to moderate chest pain and one patient in the 2.6 mg/day group after being diagnosed with a severe malignant mixed Müllerian tumor which resulted in death 2 months after discontinuation. Of the other 2 patients discontinued during the controlled period of Study O00011, one patient in the 3.9 mg/day treatment group had a severe syncope episode and severe bradycardia and one patient in the 3.9 mg/day group had severe back pain. There were no trends in SAE incidence across different treatment groups.

Reviewer's comment: *None of the serious adverse events appeared to be related to the oxybutynin TDS product.*

6.2.6 Summary of Safety Results in NDA Studies

The safety profile of oxybutynin transdermal system 3.9 mg/day (Oxytrol) was adequate for approval. The major safety issues are related to skin tolerability and anticholinergic side effects such as dry mouth and constipation.

6.3 Review of Postmarketing Safety Reports

6.3.1 Information Reviewed

The postmarketing data submitted by the Applicant which forms the basis for this review is limited to the currently approved prescription transdermal system formulations of oxybutynin. There are currently three approved transdermal formulations of oxybutynin

available, Oxytrol transdermal patch, Gelnique transdermal gel and Anturol transdermal gel.

Transdermal oxybutynin bypasses the first-pass metabolism and reduces the formation of N-desethyloxybutynin (DEO), an active metabolite of oxybutynin believed to be associated with anticholinergic side effects. The incidence of anticholinergic-related adverse events with Oxytrol is less than that reported following oral dosing of the drug. The incidences of anti-cholinergic adverse events are similar between Oxytrol administered at the approved dose of 3.9 mg/day and placebo.

Table 14 shows pharmacokinetic parameters for oxybutynin and N-desethyloxybutynin. It can be seen that the pharmacokinetics of oxybutynin are not substantially different following transdermal dosing as compared to oral dosing. However, the pharmacokinetics of N-desethyloxybutynin differs significantly. This difference is also shown graphically in Figure 1.

Table 14. Pharmacokinetic Parameters for Oxybutynin and N-desethyloxybutynin

Parameter	Oxybutynin			N-desethyloxybutynin		
	Transdermal 3.9 mg/day	Extended- release Oral 10 mg daily	P value	Transdermal 3.9 mg/day	Extended- release Oral 10 mg daily	P value
Plasma Concentration ng/ml						
C_{MAX}	4.2 ± 1.0	4.0 ± 1.5		4.9 ± 2.0	15.2 ± 6.7	
95% CI for difference	-1.0 to -1.3		0.78	-14.4 to -6.5		<0.001
AUC (ng/h/ml)						
Total*	259 ± 57	222 ± 75	0.22	321 ± 114	911 ± 427	<0.001
95% CI for difference	-25 to 98			-842 to -344		
24 Hour	10.8 ± 2.4	9.2 ± 3.3	0.22	13.4 ± 4.7	38.0 ± 17.8	<0.001
95% CI for difference	-1.1 to 4.1			-35.1 to -14.4		

* Total AUC represents the period from 0 -84 hours for transdermal and 0-96 hours for oral
Source: NDA 202211. Integrated Summary of Safety Table 6 page 34

Figure 1. Mean \pm SD steady-state oxybutynin and N-desethyloxybutynin during transdermal (left) and extended-release oral (right) administration

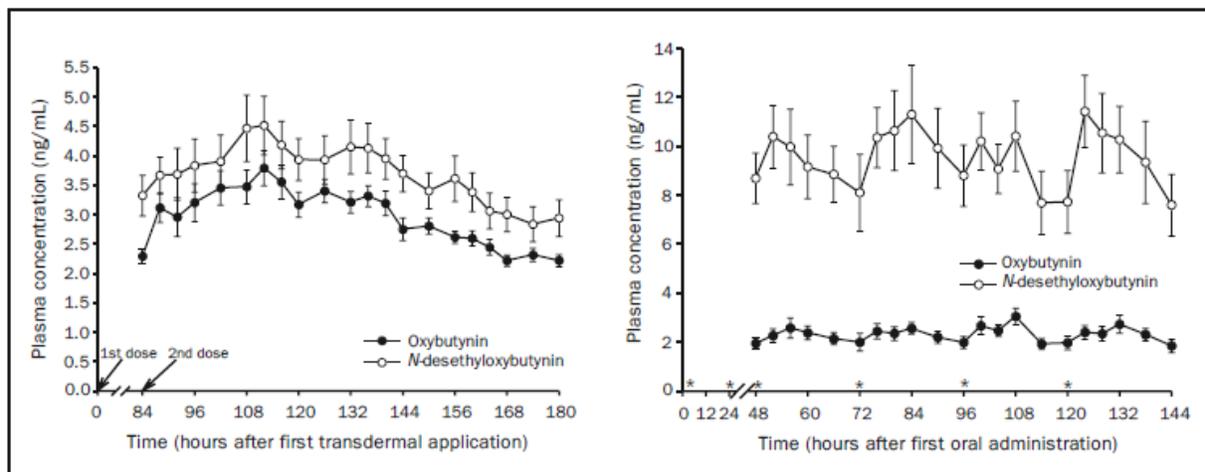


Figure 1. Mean \pm SD steady-state oxybutynin and N-desethyloxybutynin plasma concentrations (ng/mL) during transdermal (left) and extended-release oral (right) administration. * = oral tablet administration.

Source: NDA 202211. Integrated Summary of Safety Figure 1 page 33

Reviewer's Comment: *Although there are substantial postmarketing adverse event data from oral oxybutynin formulations, these were not included in this review because, as shown in the preceding discussion, the pharmacokinetic profile of these formulations differs substantially from the profile of the transdermal formulations.*

Given this significant pharmacokinetic difference in the major active metabolite and the evidence that anticholinergic events are significantly lower for transdermal formulations as compared to oral formulations, it is reasonable from a clinical perspective to evaluate adverse event information for only the transdermal formulations.

6.3.2 Summary of Periodic Adverse Event Reports (PADERS) Submitted to the Agency

From its initial launch in the US until the end of February 2011 (end period of last submitted PSUR report), IMS data estimates US sales of (b) (4) Oxytrol TDS. An additional (b) (4) Oxytrol TDS are estimated to have been sold outside of the US, providing total global sales for Oxytrol market life through 25 February 2011 of (b) (4) patches. For patients using Oxytrol TDS, the recommended dosing frequency is to use 2 patches per week, or an exposure of 104 patches per year of treatment. Hence, use of Oxytrol TDS marketed in the US represents 268,930 patient-years of treatment. Usage outside of the US accounts for 122,071 patient-years of treatment, and globally, use of Oxytrol TDS is calculated to be 391,000 patient-years of treatment.

Since its launch, 9,690 adverse events associated with the use of Oxytrol TDS in the US have been reported to the FDA in PADERS. Table 15 summarizes the adverse events that have been reported with a frequency greater than 1%.

Table 15. Adverse Events Reported in PADERS with a frequency of >1%

Organ System Class	Preferred Term	Serious Unlisted	Serious Listed	Non-Serious Unlisted	Non-Serious Listed	Total Events	% of Total Events
	Total # AEs:	204	40	3,021	6,435	9,690	
General Disorders & Administration Site Conditions	Application site erythema	0	0	0	1416	1416	14.61%
General Disorders	Application site pruritus	0	0	0	1053	1053	10.87%
General Disorders	Drug ineffective	0	0	359	601	960	9.91%
Gastrointestinal Disorders	Dry mouth	0	1	0	303	304	3.14%
General Disorders & Administration Site Conditions	Application site rash	0	0	0	246	246	2.54%
General Disorders & Administration Site Conditions	Application site irritation	0	0	1	220	221	2.28%
Eye Disorders	Vision blurred	0	0	0	196	196	2.02%
Nervous System Disorders	Dizziness	1	1	156	28	186	1.92%
Nervous System Disorders	Headache	0	0	0	172	172	1.78%
Gastrointestinal Disorders	Constipation	0	2	0	156	158	1.63%
Nervous System Disorders	Somnolence	1	1	0	154	156	1.61%
Gastrointestinal Disorders	Nausea	0	2	1	142	145	1.50%
General Disorders & Administration Site Conditions	Application site pain	0	0	20	112	132	1.36%
General Disorders & Administration Site Conditions	Application site burning	0	0	2	116	118	1.22%

Source: NDA 202211. Integrated Summary of Safety Table 13 page 74.

Application site events accounted for approximately 42% of all reported events. Gastrointestinal events were 11.5% of the events, with dry mouth (3.1%) and constipation (1.7%) representing a major portion. Nervous system disorders represented 7.7% of the events with dizziness (2%), headache (1.8%) and somnolence (1.6%) being the most frequent in this category

The incidence of events was reasonably low. Application Site Events, the most frequently reported event, occurred approximately 154 times per 10,000 pt-years of exposure.

Reviewer's Comment: *The adverse events reported during the post marketing period are similar and consistent with those reported during the phase 3 trials.*

Serious Adverse Events

There have been a total of 204 serious unlisted and 40 serious listed events reported in the PADERs for Oxytrol. There are 159 preferred term serious AEs listed, the vast majority of both listed and unlisted serious AEs are single occurrence events, which cannot be analyzed as having, or not having association with Oxytrol treatment. Only 17 unlisted serious AEs had 3 or more occurrences, while these contribute significantly to the percent of all serious AEs, they are a very small percent of total AEs, and represent incidences between 1 and 2 events likely occurring over 100,000 patient-years of product use.

For unlisted serious AEs, the most frequent events are convulsion (6 events), death and cerebrovascular accident (stroke) (5 events each), falls, and tactile or visual hallucinations (4 events each), and condition becoming aggravated, confusional state, transient blindness, faecaloma, chest pain, pain, urinary tract infection, auditory hallucination, personality disorder, dyspnea, and respiratory failure (3 events each). All reported cases of convulsion, death, cerebrovascular accident, transient blindness, faecaloma, tactile hallucination, and respiratory failure are reported as serious AEs.

Other events are reported both as serious and non-serious AEs, with differing proportions of the events being judged as serious. A total of 4 events for auditory hallucination are reported with 3 being rated as serious (75%). Four of 7 reports for visual hallucination (57%), 3 of 6 reports of personality disorder (50%), and 3 of 7 reports for pain are listed as serious AEs (43%). The other serious unlisted AEs represent a smaller percent of the individual preferred term item listings. Serious AEs for falls (4 of 16 events), chest pain (3 of 14 events), dyspnea (3 of 16 events), confusional state, (3 of 27 events), urinary tract infection (3 of 27 events), and condition aggravated (3 of 81 events), represent 25%, 21%, 19%, 11%, 11%, and 4% of the total for these AEs.

There are fewer listed serious AEs. Among these are 10 of 16 total episodes of increased sweating (62.5% of reported events), and 2 episodes each of overdose, disorientation, constipation and nausea, which account for 29%, 20%, 1%, and 1% of these reported AEs, respectively.

Reviewer's comment: *It is unlikely that any of the serious AEs are due to Oxytrol. None of these events led to a change in product labeling or warnings with the exception*

of “dizziness” which was added to the Precaution and Adverse events, Postmarketing Surveillance portions of the US labeling in 2006. In 2011 the US labeling was updated to add a warning about angioedema, which has been reported in association with oral oxybutynin use. In 2012 the US labeling was updated to add a warning about somnolence, which has been reported with oxybutynin use.

Other Postmarketing Safety Information Reviewed

The Sponsor of the original NDA submitted a summary of the safety information that has been submitted to European Regulatory Agencies and the information submitted to the FDA regarding Gelnique transdermal oxybutynin gel. The Sponsor also summarized the information contained in the FDA AERS database and the WHO Vigibase AE Database.

Reviewer’s Comment: The leading adverse events reported in this additional safety information are site administration reactions from the transdermal patch and anticholinergic side effects such as dry mouth, blurred vision, constipation, dizziness and somnolence. These data sources do not identify any significant safety issues beyond those that are seen in the US PADER analysis.

Conclusions Regarding Post Market Safety

In this reviewer’s opinion, the postmarketing safety data indicates that the most common adverse events seen with the use of Oxytrol are skin reactions and anticholinergic side effects such as dry mouth and constipation, as well as headache, dizziness and somnolence. These events are discussed in the approved product label. Somnolence was recently added to the label based on the postmarketing data for anticholinergic products (October 2012).

Adverse events associated with the use of Oxytrol are generally non-serious and occur infrequently. Even the more frequent AEs, such as skin reactions, occur with relatively low frequency based on population exposure.

In summary, my review of postmarketing data has not revealed any new safety concerns. All available safety information continues to indicate that Oxytrol remains a safe product for the treatment of the symptoms of overactive bladder.

6.4 Potential Safety Issues Relating to Delayed Diagnosis of Significant Medical Conditions

Overactive bladder (OAB) is a condition characterized by a sudden, uncomfortable need to urinate with or without urine leakage usually with daytime and nighttime frequency. The primary symptoms of OAB are urinary frequency and urgency, with or without urge incontinence. These symptoms are shared by other medical conditions and diseases, and an important medical consideration is whether or not a consumer could possibly

mistake symptoms of an undiagnosed condition for OAB, thereby delaying diagnosis and treatment of a potentially more serious condition.

In addition, as this over-the-counter product is indicated for use in women only, this section will focus on issues specific to the intended target population of women.

Reviewer's Comment: *A prospective user with only OAB like symptoms could potentially have undiagnosed urinary tract infection, diabetes, bladder cancer or pregnancy. Treating these patients for OAB may delay definitive diagnosis or unnecessarily expose users to potential risk of anticholinergic therapy. This section will analyze each of these conditions as they relate to the potential risk associated with delayed diagnosis.*

6.4.1 Diabetes Mellitus Type 2

6.4.1.1 Epidemiology

Diabetes mellitus (DM) refers to a group of common chronic metabolic disorders that share the phenotype of hyperglycemia. Type 1 DM most commonly arises in children and in young adults. Type 2 DM occurs predominantly in adults and is significantly more common (90% of DM patient in the United States). The worldwide prevalence of DM has risen significantly over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030.

In the United States, the Centers for Disease Control and Prevention (CDC) estimated that 20.8 million persons, or 7% of the population, had diabetes in 2005 (~30% of individuals with diabetes were undiagnosed). Approximately 1.5 million individuals >20 years of age were newly diagnosed with diabetes in 2005. DM increases with age. In 2005, the prevalence of DM in the United States was estimated to be 0.22% in those <20 years and 9.6% in those >20 years. In individuals >60 years, the prevalence of DM was 20.9%. The prevalence is similar in men and women throughout most age ranges (10.5% and 8.8% in individuals >20 years) but is slightly greater in men >60 years. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be 45-64 years of age.

Epidemiological data suggests that there are currently over 19 million people in the US with diagnosed diabetes, 7 million with undiagnosed diabetes and 79 million with prediabetes². Of the approximately 1.9 million patients over 20 years of age who were diagnosed with diabetes in 2010, approximately one half were woman.

² American Diabetes Association. 2011 National Diabetes Fact Sheet. Released January 26, 2011.

6.4.1.2 Symptoms of Diabetes

Increased urination frequency (polyuria) and increased thirst (polydipsia) may be presenting symptoms in some patients with type 2 DM. Hyperglycemia causes a diabetic to produce a high volume of glucose-containing urine. This results in rapid filling of the bladder and results in the frequent need to urinate in DM patients. In DM the increase in urination is usually also associated with increased thirst and other symptoms (including polyphagia, unexplained weight loss, fatigue, blurred vision etc). The combination of polyuria and polydipsia is considered a classic symptom of this disease.

In diabetic patients presenting with these symptoms, the symptoms could be mistakenly attributed to OAB by a consumer. While a medical professional would be attuned to the other symptoms that accompany the urinary frequency, the consumer may interpret the frequency as OAB.

The Applicant conducted a retrospective study (CL2010-08) designed to determine the point estimate of primary presenting symptoms consistent with OAB including urinary urgency, frequency, and/or incontinence leading to a diagnosis of UTI, Diabetes Mellitus, or Bladder Cancer in women. The study analyzed medical records of female patients, aged 18 to 85 years, having an initial (new) diagnosis of UTI, diabetes mellitus (DM), or BC. The primary objective was to evaluate the incidence of female patients aged 18 to 85 diagnosed with UTI, DM, or BC who presented with an initial primary complaint consistent with OAB.

There were a total of 1,599 medical records available for analysis, of which 609 were patients with newly diagnosed diabetes. Each of these 609 records was reviewed by two clinicians who evaluated the patient's presenting symptoms. The clinicians then recorded whether they believed that the presenting symptoms would have been consistent with a diagnosis of overactive bladder. This study showed that 1.5% to 6.4% of women newly diagnosed with diabetes had presented with symptoms similar to those of OAB.

Other patients have an insidious onset of hyperglycemia. These patients are initially asymptomatic, and are diagnosed based on results of routine laboratory tests which identify hyperglycemia. Chronic skin infections, generalized pruritus and symptoms of vaginitis are frequently the initial complaints of women with DM. These patients are not likely to confuse their symptoms with those of OAB.

6.4.1.3 Consequences of Treatment of Symptoms of Diabetes with Oxytrol for Women

The underlying physiological cause of increased urination in persons with diabetes and OAB are different. In diabetes the cause is increased urinary volume secondary to glycosuria. In OAB the cause is related to instability of the detrusor musculature that results in increased voiding.

Treating a diabetic with an anticholinergic medication is not likely to change their urinary symptoms. The glycosuria will continue to cause increased urinary volume with resulting increased frequency. The anticholinergic effect on the normal bladder musculature is unlikely to decrease the frequency.

Reviewer's Comment: *The active drug substance (oxybutynin) in Oxytrol for Women is not contraindicated in patients with diabetes and it has no effect on blood glucose. Therefore, the risk of using Oxytrol for Women to initially treat the symptoms of diabetes is limited to the consequences of delaying the definitive diagnosis and instituting appropriate therapy.*

6.3.1.4 Discussion

The Applicant's study (CL2010-08) of the frequency with which female patients with undiagnosed diabetes present primarily with symptoms of urinary frequency showed that between 1.5% to 6.4% of newly diagnosed women present with symptoms similar to those of OAB. If this is applied to the approximately 750,000 adult women who are diagnosed with diabetes yearly, we see that approximately 11,250 – 48,000 women with undiagnosed diabetes may present with urinary symptoms yearly.

This group of women is the group that could potentially mistakenly use over-the-counter Oxytrol for Women to treat the urinary symptoms. The consequences of this inappropriate treatment would be a delay in diagnosis and institution of appropriate therapy. The delay would in most cases be short since the Oxytrol for Women treatment should not change the symptoms of frequent urination. The likelihood of a delay in the diagnosis of a serious case of diabetes, such as with diabetic ketoacidosis, would appear to be small since other symptoms would be more prominent in that serious situation.

In conclusion, there is a small to moderate sized group of women who could mistakenly take Oxytrol for Women to treat the urinary symptoms of undiagnosed diabetes. The consequences of that inappropriate treatment should in most cases be limited to delay in diagnosis. The possibility of this delay in diagnosis resulting in serious morbidity would appear to be unlikely but cannot be totally ignored.

6.4.2 Bladder Cancer

6.4.2.1 Epidemiology of Bladder Cancer

Bladder cancer (BC) is the second most common urological cancer and is primarily a disease observed in elderly individuals. The mean age of patients at diagnosis is 65 years. BC occurs more frequently in men than women (2.7:1). A 2010 patient-oriented publication from the National Cancer Institute of the NIH, "What You Need to Know

About Bladder Cancer”, reports that about 52,000 and 18,000 new cases of bladder cancer are diagnosed in men and women (respectively) annually, with most patients being over 70 years of age.

6.4.2.2 Presentation of Bladder Cancer

Hematuria is the primary presenting symptom in 80-90% of patients with bladder cancer. Most often the hematuria is gross and microscopic hematuria accounts for only about 2% of bladder cancer. Irritative symptoms similar to cystitis (Increased frequency, urgency of micturition and dysuria) are the next most common presentation for bladder cancer.

The Applicant’s study CL2010-08 designed to evaluate the frequency with which patients newly diagnosed with bladder cancer, diabetes or UTI presented with symptoms similar to those of OAB was discussed in section 6.4.1.2 of this review. In this study there were a total of 1,599 medical records available for analysis, of which 284 were patients with documented bladder cancer. Each of these 284 records was reviewed by two clinicians who evaluated the patients presenting symptoms. The clinicians then recorded whether they believed that the presenting symptoms would have been consistent with a diagnosis of overactive bladder. Of the 284 bladder cancer patients whose records were evaluated, 21 patients had symptoms that at least one clinician felt were consistent with the predefined definition of OAB (point estimate: 7.39%; 95% CI: 4.75% - 11.24%).

The National Cancer Institute has estimated that there will be approximately 73,500 new cases of bladder cancer diagnosed in the United States in 2012. Of these cases they estimate that 17,900 will be in women³. With this information we can estimate that $(0.0739 * 17,900)$ 1,320 women who will be diagnosed as having bladder cancer will present with the symptoms of overactive bladder yearly. This is a group that would be at risk for using over-the-counter Oxytrol for Women inappropriately, thus delaying the making of the correct diagnosis.

6.4.2.3 Consequences of Treatment of Symptoms of Bladder Cancer with Oxytrol for Women

The underlying physiological cause of increased urination in persons with bladder cancer and OAB are different. In bladder cancer the cause would likely be irritation of the bladder transitional cell lining by the tumor. In OAB the cause is related to instability of the detrusor musculature that results in increased voiding.

Treating a patient with bladder cancer with an anticholinergic medication is not likely to change their urinary symptoms. The tumor will continue to cause localized irritation and

³ National Cancer Institute, Surveillance Epidemiology and End Results, SEER Stat Fact Sheets:Bladder.

is likely to be associated with other symptoms such as hematuria. The anticholinergic effect on the normal bladder musculature is unlikely to decrease the frequency of urination in these patients.

Reviewer's Comment: *Oxybutynin is not contraindicated in patients with bladder cancer and it has no known tumor promoting effects. Therefore, the risk of using Oxytrol for Women to treat the symptoms of bladder cancer is limited to the consequences of delaying the definitive diagnosis of the tumor and instituting appropriate therapy.*

The impact of a delay in diagnosis is difficult to quantify. The impact would certainly be influenced by the length of the delay. With anticholinergic treatment, it is unlikely that a patient will have a significant improvement in their irritable voiding symptoms. It is reasonable to estimate that the delay in diagnosis caused by inappropriate treatment with Oxytrol for Women would, in the large majority of cases, be short.

6.4.2.4 Discussion

There is a small group of women, roughly estimated to be on the order of magnitude of 1,300 per year, who present with symptoms of bladder cancer that are similar to the symptoms of overactive bladder. These women could potentially use over-the-counter Oxytrol for Women inappropriately and thus delay the making of a correct diagnosis and the implementation of appropriate therapy for the cancer. The impact of this delay is difficult to precisely characterize. It is reasonable to consider that the impact of the delay would be dependent on the length of the delay.

When a patient inappropriately uses Oxytrol for Women to treat the symptoms of bladder cancer, we can predict that the symptom relief would be minimal. Therefore, the Oxytrol for Women related delay is likely to be short. While the effect of any delay in diagnosis of any cancer should not be minimized, it is reasonable to estimate that the use of Oxytrol for Women in this condition is not likely to result in a major delay in most cases.

6.4.3 Urinary Tract Infection

6.4.3.1 Epidemiology of Urinary Tract Infection

UTI is a common condition, especially among women. Uncomplicated UTIs are the second most common type of systemic infections, and account for over 8 million physician visits annually. Lifetime prevalence of UTIs among women is approximately 50% and one in three women can expect to experience a lower UTI requiring antimicrobial treatment before middle-age. In a given year UTI is estimated to affect about 10 million US adults.

The risk factors for UTI include:

- female gender
- being sexually active
- women who use a diaphragm with spermicidal drugs for birth control (as opposed to other methods such as OCP, IUD)
- menopause
- urinary tract abnormalities or blockages which impede normal urine flow (structural abnormalities, kidney stones, BPH)
- immunosuppression
- requiring a catheter for urination

6.4.3.2 Presentation of UTI

Common symptoms of lower urinary tract infections are:

- a strong and persistent urge to urinate;
- frequent urination associated with passage of small amounts of urine
- a painful or burning sensation in the area of the bladder and urethra associated with passing urine
- urine appearing cloudy and/or having a strong or foul odor
- urine which can appear bright red, pink or dark – due to blood in urine
- pressure or pain in the pelvic area

While the symptoms of urinary frequency and urgency are common to both lower urinary tract infections and overactive bladder, the remaining symptoms of UTI are not characteristic of overactive bladder.

The Applicant's study CL2010-08 designed to evaluate the frequency with which patients newly diagnosed with bladder cancer, diabetes or UTI presented with symptoms similar to those of OAB was discussed in section 6.4.1.2 of this review. In this study there were a total of 1,599 medical records available for analysis, of which 706 were patients with documented UTI. Twenty of the 706 patients were considered by at least one of the two reviewers to have presenting symptoms consistent with the definition of OAB. This provides a point prevalence of 2.83% (95% CI: 1.78 – 4.42%). This study indicates that the proportion of women with newly diagnosed UTI who present with symptoms similar to those of OAB is reasonably low, on the order of 3%.

6.4.3.3 Discussion of Oxytrol for Women and UTI

OAB is a chronic syndrome which develops gradually over time. In contrast, a typical UTI is an acute event, with rapid onset of symptoms, and when effectively treated with an appropriate antibiotic therapy, has rapid resolution. UTIs occur mostly in patients who have a normal, unobstructed genitourinary tract and the symptoms in

uncomplicated UTIs are mostly confined to the lower urinary tract. UTIs are most common in young, sexually active women; a high incidence of UTI is also seen in older women. Patients having a UTI most commonly present with dysuria, urinary frequency, urinary urgency, and/or suprapubic pain.

Different pathophysiology of UTIs and OAB is reflected in different treatment approaches. Standard treatment for UTIs is aimed towards elimination of the infectious agent using a course of antibacterial therapy. Antimuscarinic agents used to treat OAB are not therapeutic for treatment of UTIs. Although antimuscarinic agents may reduce frequency and urgency associated with UTI, they will not eradicate the pathogenic organisms or mask other UTI related symptoms (i.e. pain and burning during urination etc). Oxytrol for Women will not effectively treat symptoms of UTI, including those of urinary frequency and urgency. The physiological mechanism of urinary frequency and urgency in UTI is not due to enhanced muscarinic activation of the bladder detrusor muscle but due to an inflammatory response from the underlying infection.

Reviewer's Comment: *If a patient inappropriately uses Oxytrol for Women to treat the symptoms of a UTI it is unlikely that the symptoms will change significantly. The patient would be unlikely to continue Oxytrol for Women beyond a short number of days. They would then be expected to seek medical evaluation of their symptoms.*

It is possible that the infection could worsen during the period the patient is taking Oxytrol for Women. The signs of a worsening UTI would not be similar to the symptoms of overactive bladder. The patient might experience dysuria, fever or back pain. These symptoms would be likely to cause the patient to seek medical evaluation.

6.4.4 Pregnancy

An important medical consideration is whether use of Oxytrol for Women could potentially delay the diagnosis of pregnancy. This could occur if the primary pregnancy symptoms being experienced by the consumer are those of urinary frequency and urgency, and the consumer chooses to treat the symptoms with Oxytrol for Women.

6.4.4.1 Discussion of Voiding Symptoms in Pregnancy and OAB

The Applicant has stated, and this reviewer agrees, that it is unlikely that the change in urinary frequency and urgency which occurs during pregnancy would be confused with the symptoms of OAB. The changes in urinary frequency which occur in pregnancy are very likely to be associated with a number of other pregnancy-related symptoms. These pregnancy related symptoms include lower back discomfort, breast tenderness and enlargement, constipation, nausea and vomiting, heartburn and indigestion, changes in menstrual cycle, weight gain and body changes. Furthermore, pregnancy-associated urinary symptoms are related to fetal growth, and would be likely to change according to

the maturation stage of pregnancy. The symptoms of OAB would be unlikely to show this progression.

Reviewer's Comment: *The decision by a consumer to use Oxytrol for Women to treat the common urinary symptoms of a known pregnancy cannot be ruled out, but can likely be minimized by appropriate labeling.*

6.4.4.2 Oxybutynin Drug Facts Relative to Use during Pregnancy

Prescription labeling for Oxytrol (oxybutynin transdermal patch) lists the drug as pregnancy category B. In standardized *in vitro* and *in vivo* studies in mice, rats, hamsters and rabbits, the active drug substance, oxybutynin, did not have mutagenic activity nor did it demonstrate evidence of impaired fertility or harm to the fetus. No direct safety studies have evaluated Oxytrol in women who are or who are likely to become pregnant. The current prescription label recommendation is that Oxytrol not be prescribed to women who are pregnant, unless, in the judgment of the physician, the possible clinical benefits outweigh possible hazards.

6.4.4.3 Impact of Delaying the Diagnosis of Pregnancy by the Use of Oxytrol for Women

As discussed in the paragraphs above, it is not likely that Oxytrol for Women would contribute to a significant delay in the diagnosis of pregnancy. The voiding symptoms associated with pregnancy constitute a relatively small portion of the symptoms associated with pregnancy and they are unlikely to respond well to Oxytrol for Women therapy. Therefore it is unlikely that a significant delay in diagnosis would result from Oxytrol for Women use.

Also as discussed in the preceding paragraphs, the use of Oxytrol for Women during pregnancy has not been shown to have adverse effects on the fetus.

The impact of the use of Oxytrol for Women to treat the voiding symptoms associated with pregnancy is likely to be a short delay in instituting appropriate prenatal care in a small number of individuals.

6.4.5 Reviewer's Conclusions Regarding Delayed Diagnosis

*With respect to the conditions evaluated above, **diabetes, bladder cancer, urinary tract infection**, it is reasonable to conclude that the delay in diagnosis caused by the inappropriate use of Oxytrol for Women to treat the symptoms of the condition would be a relatively short one. Also, it is unlikely that a delay caused by this inappropriate use of Oxytrol for Women would have a significantly adverse effect on the condition, impair the eventual correct treatment or alter the course of the disease.*

For pregnancy, although it is possible that there could be a delay in diagnosis, it is unlikely that there would be a significant clinical consequence on the mother or fetus.

7. Reviewer's Concluding Statement

Oxybutynin Transdermal System 3.9 mg/day (Oxytrol) was shown to be an effective treatment for the symptoms of overactive bladder based on the results of two phase 3 studies that were performed by the Sponsor of NDA 21-351 and that were reviewed at the time of the submission of that NDA in 2003. Based on these studies Oxytrol had meaningful clinical efficacy in improving urinary incontinence, urinary frequency and the average void volume.

The safety data submitted with NDA 21-351 showed that the major adverse events associated with the use of Oxytrol are skin reactions and anticholinergic side effects such as dry mouth, constipation and dizziness. These events were reasonably infrequent and of generally mild to moderate severity. The available Postmarketing information that has accumulated since the approval of Oxytrol in 2003 has not changed this safety profile.

Based on the pre-approval and the post-approval data this reviewer has found no evidence that would change the Division's prior conclusion that Oxytrol is a safe and effective treatment for overactive bladder.

8. Addendum - Advisory Committee

A summary of overactive bladder, its diagnosis and treatment was presented by this reviewer to the Nonprescription Products Advisory Committee on November 6, 2012. This presentation also included a brief discussion of the clinical information that supported the approval of Oxytrol as a prescription product in 2003. Reviewers from the Division of Nonprescription Clinical Evaluation also presented a summary of the self-selection, label comprehension and actual use studies that the Sponsor has submitted to support the switch of Oxytrol to a nonprescription product.

Following extensive discussion, five committee members voted that the information submitted adequately supported the nonprescription conversion and six members voted that it did not. The committee's discussion centered on the adequacy of the labeling to assure appropriate patient self-selection and safe use of the product.

The committee's discussion will be considered as the product labeling is evaluated and edited by DNCE.

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/s/

DONALD R MCNELLIS
12/17/2012

SURESH KAUL
12/17/2012
I concur with Dr. McNellis's review.

CLINICAL REVIEW

Application Type	NDA (505(b)(1))
Application Number(s)	202211
Priority or Standard	Standard
Submit Date(s)	March 26, 2012
Received Date(s)	March 26, 2012
PDUFA Goal Date	January 26, 2013
Division / Office	DNCE/ODE IV
Reviewer Name(s)	Ryan Raffaelli, M.D.
Review Completion Date	November 18, 2012
Established Name	Oxybutynin Transdermal System
(Proposed) Trade Name	Oxytrol for Women®
Therapeutic Classes	Antispasmodic, anticholinergic
Applicant	MSD Consumer Care, Inc.
Formulation(s)	Transdermal Film – Extended Release (3.9 mg/day)
Dosing Regimen	One patch applied up to twice weekly (every 4 days)
Indication(s)	Treats overactive bladder in women
Intended Population(s)	Women over age 18

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This is the clinical review evaluating MSD Consumer Care's (MCC, the sponsor, the applicant) proposal to partially switch Oxytrol® (3.9 mg/day, oxybutynin transdermal system) from prescription (Rx) to Over-the-counter (OTC) marketing status as Oxytrol for Women® (proposed tradename). This is a partial switch because the drug product will remain Rx for use by men for the same indication. **Based on my review of the available data from the clinical perspective, I recommend approval** contingent on the applicant accepting labeling recommendations to support safe and proper use of Oxytrol for Women® in the OTC setting.

My recommendation is based on assessment of the results of the Actual Use Study (AUS), Consumer Trial of Oxytrol® (CONTROL; Protocol #CL2008-13), and safety data from other postmarketing studies, overall postmarketing experience and published scientific data. The AUS was adequately conducted with an appropriate number of enrolled subjects (n=1069), purchasers (n=855) and users of at least one application of the drug (n=785). Median exposure to the test drug was 45 days, with mean exposure of 44.6 +/- 23 days. This is similar to current, predicted drug utilization in the Rx setting where most patients appear to use the drug for 1-2 months for any treatment episode. There were 727 verified users, and 58 non-verifiable users, meaning there was missing diary data from subjects reporting that they used the drug, or users did not complete an interview.

The applicant met the *a priori* misuse threshold for the CONTROL trial, supporting proper use. The applicant established the primary endpoint to assess the proportion of subjects who had new symptoms or worsening overactive bladder (OAB) symptoms, as per the Drug Facts label, but who did not stop use to seek further medical evaluation. Misuse was mitigated based on interview responses. Overall, the mitigation strategies were reasonable. The trial was powered to adequately assess this endpoint. **The threshold was set at ≤ 5%, and the post-mitigation misuse rate in the trial, by the primary endpoint, was 3.4% (95% CI; 2.2, 5.0).** Other major secondary endpoints included the proportion of subjects who did not stop use after two weeks without improvement in OAB symptoms (secondary endpoint 3; SE3) and the proportion of subjects who either used any patch for longer than directed (> four days) or used more than one patch simultaneously (secondary endpoint 5; SE5). There were three minor secondary endpoints (1, 2 and 4), the results of which did not affect my analysis.

However, whether a drug is appropriate for a switch to OTC marketing does not rely solely on assessment of consumer behavior endpoints. In the CONTROL trial, evaluation of diary entries and interpretation of subjects' responses to interview

questions allowed for further assessment of the adequacy of the proposed Drug Facts label to support safe and proper use. I evaluated interview responses in the context of the subjects' primary urinary symptoms, medical history, new or worsening symptoms over the course of the trial, use of the drug, and patterns of follow up with their healthcare providers.

Misuse by the primary endpoint, SE3 and SE5 underwent mitigation processes since such misuse, addressed in follow up interviews and determined by diary entries, could be interpreted in ways to still consider it appropriate use. The processes entailed full review of the Case Report Forms (CRFs) of all misusers by these endpoints. For example, a misuser who reported worsening OAB symptoms to their physician, and who was told to continue using the drug, should not be included in the misuse proportion (see **Sections 6.1.4 Analysis of Primary Endpoint** and **6.1.5 Analysis of Secondary Endpoints(s)**). As stated above, subjects' post-mitigation misuse rate was within the target threshold for the primary endpoint. The pre-mitigation misuse rate was 14% for the primary endpoint. The proportion was derived from all verified users who used at least one patch (n=727). While the trial was powered to assess this rate, the applicant also calculated a post-hoc proportion of a subgroup who misused out of those users who reported new symptoms or worsening OAB symptoms. Here, 72% of verified users misused the drug, pre-mitigation, while the post-mitigation rate was 17.7%. Although the trial was not powered to assess this rate, it may have more clinical significance than the rate of misuse from all those who used the patch.

Similarly, misuse rates by SE3 were much higher when the denominator included only those subjects who reported no improvement. The applicant determined misuse by SE3 as 22.6%, pre-mitigation, and 11%, post-mitigation, of all those who used the drug for two weeks and completed the week 3 interview. The proportion of a subgroup for SE3 was 77.5%, pre-mitigation, and 38%, post-mitigation, out of only those subjects who reported no improvement of their OAB symptoms after two weeks of use. For SE5, the pre-mitigation misuse rate was 51% while the rate declined to 20.9%, post-mitigation. I believe the mitigation strategies for these endpoints were reasonable. See **Section 6 Review of Efficacy** for summary of all the major endpoints.

This reviewer also assessed the impact on subjects' use decisions based on their demographics, presenting urinary symptoms, adverse events or medical diagnoses reported at enrollment, or made over the course of the trial. Consideration of the impact helped determine whether the drug can be safely and properly used in the OTC setting.

The design of the study was adequate. The age range of subjects in the study was also appropriate (18-94 years). Non-white subjects accounted for almost 23% of the population, and subjects over 65 years of age and 75 years of age accounted for 32.7% and 16.6%, respectively. Low literate subjects made up over 13% of the population. The demographics were adequate. Subjects were excluded from the Use phase of the trial if they:

Clinical Review

Ryan Raffaelli, M.D.

NDA 202211

Oxytrol for Women® (Oxybutynin Transdermal System 3.9 mg/day)

- were male
 - were pregnant or suspecting of pregnancy
 - were breastfeeding
 - reported having narrow angle glaucoma
 - had an allergy to oxybutynin
 - had hematuria unrelated to menses
 - had back or flank pain with fever, and either hematuria, dysuria or cloudy, foul-smelling urine (symptoms of UTI)
- } Excluded from enrolling

Only 1.8% of the total number of subjects screened was male (n=45), pregnant or suspecting of pregnancy (n=5). The investigator did not question why these subjects wished to participate in the trial. Of those enrolled in the trial, 27, or 12.6% of subjects who made a decision to purchase the drug, were excluded due to the above medical reasons and referred to their physician. The most commonly reported reason for medical exclusion was hematuria unrelated to menses (n=13). No subjects had a positive pregnancy test. Only four subjects (2.5%) who decided not to purchase the drug would have been excluded for medical reasons. Of the excluded subjects who made a decision to purchase, several received medical diagnoses after termination from the trial. These included UTI (n=2), pre-diabetes, type 2 diabetes, kidney stones and irregular menstrual bleeding. I reviewed the reasons why these excluded subjects decided to purchase the drug, and it does not appear that the label warnings were misunderstood or ignored to any great degree.

Over 78% of subjects who chose to purchase the drug had label ineligibilities (see **Table 10**). Some ineligibilities are reflective of serious alternative diagnoses, e.g., urinary tract infection (UTI), bladder cancer, diabetes, and pregnancy, that may present with OAB symptoms and should be understood since OAB is a diagnosis of exclusion.. Some of these alternative conditions, such as UTI, bladder cancer, and pregnancy, more typically present with other signs or symptoms. Diabetes may be otherwise asymptomatic, but this is common even in clinical practice, and available data do not show that diagnosis would be delayed by OTC availability of oxybutynin. Other ineligibilities identify absolute contraindications (urinary and gastric retention and narrow angle glaucoma). The proposed label has been revised to signal to consumers that they should have medical diagnosis of these conditions. Consumers who know they have these diagnoses are more likely to notice the warnings, choose not to use the drug, and seek professional advice.

Subjects with many ineligibilities were allowed to purchase and use the drug because the clinical consequences of use may not be significant (stress incontinence, weight loss, use of diuretics), and the applicant wanted to evaluate how the label might be understood and acted upon in a “real world” setting. The most frequently reported (42.8% of purchasers) ineligibility was a feeling of incomplete bladder emptying to reflect urinary retention, followed by diabetes risk factors (42.5%, family history of diabetes or OAB symptoms with excessive thirst, extreme hunger or increased

tiredness) and stress incontinence (32.9%). Subjects reporting incomplete bladder emptying may have been attempting to explain their symptoms. That only three of these subjects spoke with their doctors prior to use indicates that subjects misunderstood the label warning. The warning revision is described above.

Whether users met the OAB symptom conditions of the proposed indication (two or more symptoms of either urinary urgency, urinary frequency or urge incontinence for at least three months) was another ineligibility I considered. FDA previously agreed with the applicant that the proposed indication was reasonable. Most subjects met the symptom conditions. Over 60% of all users reported already having a diagnosis of OAB. Of those who did not meet the symptom conditions, 22 (12.3%, 22/179) reported having been told by their doctors that they had OAB. Eleven used the drug. It appears that OAB symptoms are easily recognizable by consumers.

At the weeks 3, 7 or 12 follow up interviews, the majority of subjects, initially reporting potentially serious ineligibilities, reported improvement in OAB symptoms:

- At least 65% with incomplete bladder emptying
- Nearly 70% with possible UTI symptoms (fever or chills with dysuria OR hematuria with menses OR back or flank pain OR cloudy, foul-smelling urine, but none in combination)
- At least 63.5% with diabetes risk factors

While the rates of improvement appear high for those who may have had alternative diagnoses or serious conditions, interpretation may be limited by the total number of users completing these interviews and other factors. The total number of subjects completing interviews steadily declined over the duration of the trial. One could suppose that users who were doing well in the trial may have been more likely to participate in the interviews. However, improvement also indicates that consumer uncertainty may exist when attempting to distinguish between idiopathic OAB and other diagnoses. OAB symptoms due to other disease processes such as UTI or diabetes may partially respond to anticholinergics like oxybutynin in the short term. Also, idiopathic OAB may coexist with UTI or diabetes and respond to anticholinergics. While use of the drug could theoretically delay diagnosis of other, more serious conditions, the available data do not reveal that delays exist. See **Section 1.2 Risk Benefit Assessment** for further discussion.

1.2 Risk Benefit Assessment

Overactive bladder (OAB) is a complex of symptoms defined by the International Continence Society. The definition is urinary urgency, frequency and nocturia, with or without urge urinary incontinence – involuntary urine leakage accompanied by or preceded by urgency to micturate. The definition requires the absence of urinary tract

infection or other obvious pathologic condition¹, making OAB a diagnosis of exclusion based only on clinical symptoms. According to the applicant, and as a result of my review, the symptoms are clearly recognizable by women who have them. The symptoms are well known to negatively impact patients' daily living, self-image and quality of life. In the Actual Use Study (AUS), CONTROL, subjects in the trial overwhelming indicated that their OAB symptoms were significantly affecting their lives. Prevalence of symptoms increases with increasing age, as does the prevalence of alternative diagnoses with similar urinary symptoms, e.g., diabetes mellitus, UTI, bladder cancer. Delayed or missed diagnosis of prostate disease was a safety concern with use of the drug by males. For safety reasons, a healthcare professional should evaluate whether OAB symptoms in males were due to prostate cancer or benign prostatic hyperplasia. Therefore, the proposed product will only be marketed to women in the OTC setting.

There is a significant need for pharmacologic therapy for OAB, particularly after conservative measures have not achieved the patient's desired effect. Conservative measures include behavioral therapies, e.g., bladder training, pelvic floor muscle training and fluid intake management. Prevalence of the diagnosis is reasonably high and likely to increase as the elderly population continues to increase worldwide. Efficacy of the drug in the treatment of OAB symptoms is established. A 2009 Report from the International Consultation on Incontinence included oxybutynin in its list of efficacious drugs with acceptable tolerability and safety profiles. Current understanding of OAB indicates that while there is a clear need for effective OAB treatments, many women are reluctant to broach the subject with their physicians. There appears to be a stigma associated with symptoms. OTC availability and increased access could be of benefit to a population in need.

Of nearly 14,000 AEs reported in the NDA holder's postmarketing pharmacovigilance database, over 40% were application site reactions, with another 12% being gastrointestinal disorders including dry mouth and constipation, frequently reported anticholinergic effects. Anticholinergic effects are not uncommon and can be quite bothersome. Further, over 96% of AEs reported in the NDA holder's database were non-serious. Data from other databases and clinical trials support these findings. See **Section 9.2 Labeling Recommendations** and **Figure 5** for incorporation of safety data into Drug Facts labeling. Such reactions and effects can be managed by simply removing the patch, since most events are self-limited, do not worsen and resolve on their own without medical intervention.

The Rx label identifies several safety topics that, ideally, should be adequately translated and understood in an OTC label. Medical contraindications to use the Rx

1 Haylen BT, D de Ridder, RM Freeman, SE Swift, B Berghmans, J Lee, et. al., 2010, An International Urogynecological Association (IUGA)/International Continence Society (ICS) Joint Report on the Terminology for Female Pelvic Floor Dysfunction, *Neurourol Urodyn*, 29: 4-20.

product include diagnosis of urinary retention or gastric retention, uncontrolled narrow-angle glaucoma and known hypersensitivity to oxybutynin, or to any of the components of Oxytrol®. As stated above, only subjects reporting glaucoma and allergy to oxybutynin were excluded from the Use phase of the CONTROL trial. There are warnings to speak with a doctor if consumers have liver or kidney disease, if they have disorders that may limit gastrointestinal (GI) motility (ulcerative colitis, myasthenia gravis) or increase risk of worsening GI disease (gastroesophageal reflux disease or esophagitis), and if they are using other anticholinergic drugs or drugs that inhibit CYP3A4 enzymes.

Additional safety precautions are proposed in OTC labeling since there is no learned intermediary helping to determine whether the drug is right for a consumer. These include warnings not to use the drug if consumers believe their OAB symptoms, or coincident symptoms, could be due to UTI, diabetes, early pregnancy or other more serious conditions. Subjects who consider alternative, more serious diagnoses are directed to see their doctors first. Whether they can and will do so is addressed in the review and in **Section 1.1 Recommendation on Regulatory Action**. Regarding UTI, the label instructs consumers not to use the product if they have pain or burning when urinating, particularly if associated with fever or chills, or if they have hematuria, back or flank pain, or urine that is cloudy or foul-smelling. While there were several UTIs, including a few serious cases, diagnosed during the CONTROL trial, few were diagnosed in subjects who had possible UTI symptoms at enrollment, or in subjects reporting new non-OAB symptoms in the Use phase. Those subjects with symptoms appeared to easily recognize them, prompting quick medical evaluation for diagnosis. Those subjects diagnosed with UTI without having reported significant symptoms are more difficult to evaluate. Some diagnoses were made only at the end of the study when subjects followed up with their physicians after being informed that their End-of-Study (EOS) urinalysis was positive.

Subjects may not consider that their OAB symptoms are linked to UTI. With Oxytrol for Women® available OTC, it is not clear how many future consumers, ultimately diagnosed with UTI, would seek a medical evaluation for OAB symptoms. Less than 3% of subjects who evaluated the label reported OAB symptoms of one month or less, and most who were diagnosed with UTI reported longstanding (several months to years) OAB symptoms and had typical UTI symptoms (dysuria, pain). I would not expect most consumers to tolerate UTI symptoms beyond one month. Additionally, data from the applicant's electronic health records' study (CL2010-08; **Section 2.6**

Other Relevant Background Information) showed that most patients with UTI will present with dysuria or back and flank pain, not OAB symptoms, lending support to consumers' ability to self-recognize and distinguish their symptoms from UTI. From the postmarketing data, both the NDA holder's MATRIX trial and data from safety databases show that UTIs are not uncommon in the older, female population that is likely to use this drug, but that there are no data supporting a delay in diagnosis of UTI.

Early pregnancy, bladder cancer and diabetes are alternative diagnoses that can present with similar OAB symptoms. Pregnant women were excluded from the trial, and there were no pregnancies diagnosed over the course of the trial. As noted below, upwards of 50% of women in their first trimester may have OAB symptoms. The drug will not be effective for them. Further, while there have been no oxybutynin studies in pregnant women (the drug carries a Pregnancy category B label), and it is possible that these women would be exposed to undue risk with use, there are no postmarketing data indicating a safety signal for the women or their fetuses. The duration component of the indication (> 3 months) should also prevent most pregnant women from mistakenly choosing to use the drug, and the pregnancy warning should be adequate to inform women to seek medical advice if they are, or believe they are, pregnant.

There were no cases of bladder cancer diagnosed in the CONTROL trial, in any prior clinical trials of oxybutynin, or, in postmarketing experience, identified as having the diagnosis delayed by use of Oxytrol®. **Table 23** compares the symptoms of OAB and bladder cancer. The symptoms of bladder cancer appear to differ significantly enough from OAB to support minimal risk of delay in diagnosis. The data evaluated in this review indicate that Oxytrol for Women®, available in the OTC marketplace, will not likely lead to clinically relevant delays in diagnosis. Older men are more often diagnosed with bladder cancer and most patients present with painless, gross hematuria. While OAB symptoms can present, and may be associated with more advanced cancers, bladder cancer is generally slow-growing and the literature indicates that there are already delays in diagnosis both prior to patient's seeking medical evaluation, and prior to a physician's undertaking specific diagnostic testing¹³. Risk of delayed diagnosis should be further limited by labeling for use by consumers > 65 only on the advice of their doctors. The applicant's electronic health records' study and the postmarketing experience also support the safety of oxybutynin OTC availability.

Finally, many subjects reported diabetes risk factors at enrollment, but only two subjects were diagnosed with diabetes (one user and one subject excluded for hematuria) over the course of the trial. These subjects had longstanding OAB symptoms, one year and five years, and presented to their physicians with symptoms that the subjects believed were unrelated to diabetes. Current clinical understanding and data from the applicant's electronic health records study indicate that many undiagnosed diabetes patients are initially asymptomatic, and that many are diagnosed during routine medical and lab follow up visits with their physicians. While diabetes patients can present with increased urinary frequency and excessive thirst or hunger, they are unlikely to benefit from oxybutynin because the mechanism of symptoms differs between OAB and diabetes. These patients will likely seek medical attention as their urinary symptoms, or other non-urinary symptoms of diabetic complications, e.g., lower extremity pain, vision changes, arise or worsen. None of the available data shows that diabetes diagnosis would be significantly delayed by the availability of oxybutynin in the OTC marketplace.

Although most subjects (78.5%) chose to purchase and use the drug even though they had various ineligibilities according to the label, their use did not result in apparent delays in diagnosis of more serious medical conditions. Nor did users who reported new symptoms or no improvement of their OAB symptoms (38% of verified users; 276/727) report AEs or receive diagnoses indicating a safety signal or concern. While only 23.5% (65/276) of these users spoke with their doctors about their symptoms, 71% (46/65) of those who did were cleared to continue using the drug.

The majority of AEs reported were similar to those most frequently identified in the worldwide postmarketing data. Overall, the AUS conducted by the sponsor and the postmarketing safety data support safe use of the proposed transdermal formulation of oxybutynin in the OTC setting.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

2.1 Product Information

- Established name: Oxybutynin Transdermal System
- Proposed name: Oxytrol for Women®
- Pharmacologic classes: Antispasmodic, anticholinergic (antimuscarinic)
- Indication: Treats overactive bladder in women
- Dosing regimen: One patch² applied up to twice weekly (every 4 days) provides 3.9 mg oxybutynin per day.
- Target population: 18 years of age and older.

The applicant, MSD Consumer Care, Inc. (MCC) submitted this application for a partial Rx-to-OTC switch of Oxytrol®. The product is a prescription drug approved to treat OAB. OAB usually results in urinary incontinence and affects an estimated 1 in 11 adults, both men and women, in the U.S., and nearly 12%³ in a sample of other

² Throughout the review, this reviewer will refer to the proposed product as a “patch” rather than a “transdermal system,” although the latter designation is the approved form of the drug.

³ Irwin DE, I Milsom, S Hunkskaar, et. al., 2006, Population-based Survey of Urinary Incontinence, Overactive Bladder, and Other Lower Urinary Tract Symptoms in Five Countries: Results of the EPIC

countries. It occurs more commonly in older adults. Upwards of 50% of women report having experienced urinary incontinence at some point in their lives⁴. The first oxybutynin drug product was approved in an oral formulation in 1975. The applicant claims there are several reasons supporting a switch to OTC marketing:

- Idiopathic OAB is a bothersome, but benign condition
- OAB is self-recognizable and directions for use can be easily labeled and understood
- Oxybutynin in a transdermal formulation is safe, and without significant safety concerns
- Data supports minimal risk to mask symptoms or delay treatment of more serious diseases.

Oxytrol® was approved in February 2003. Once applied to the skin, oxybutynin is delivered consistently over a 3 to 4 day interval. The 39 cm² transdermal contains 36 mg of oxybutynin.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Approved Prescription Drugs for the Proposed Indication

Drug Product	Active Ingredient	Formulation/Dosage	Date Approved
Ditropan®	Oxybutynin chloride	5 mg tablet	July 16, 1975
Ditropan®	Oxybutynin chloride	5 mg/5 mL syrup	November 29, 1979
Botox®	OnabotulinumtoxinA	200 units intradetrusor injection	December 9, 1991
Ditropan® XL	Oxybutynin chloride – extended release	5, 10, 15 mg extended release tablets	December 16, 1998
Detrol®	Tolterodine tartrate	1 and 2 mg tablets	March 25, 1998
Detrol® LA	Tolterodine tartrate – extended release	2 and 4 mg capsules	December 22, 2000
Oxytrol®	Oxybutynin chloride	3.9 mg/day transdermal system	February 26, 2003
Sanctura®	Trospium Chloride	20 mg tablet	May 28, 2004
Vesicare®	Solifenacin Succinate	5 and 10 mg tablets	November 19, 2004
Enablex®	Darifenacin Hydrobromide – extended release	7.5 and 15 mg tablets	December 22, 2004
Sanctura XR®	Trospium Chloride – extended release	60 mg capsule	August 3, 2007
Toviaz®	Fesoterodine	4 and 8 mg tablets	October 31, 2008

Study, *Eur Urol* 50: 1306-1314.

4 Thom D, 1998, Variation in Estimates of Urinary Incontinence Prevalence in the Community: Effects of Differences in Definition, Population Characteristics, and Study Type, *J Am Geriatr Soc*, 46: 473-480.

Drug Product	Active Ingredient	Formulation/Dosage	Date Approved
	Fumarate – extended release		
Gelnique®	Oxybutynin chloride	10% topical gel (100mg)	January 27, 2009
Anturol®	Oxybutynin chloride	3% topical gel, metered (84 mg)	December 7, 2011
Myrbetriq™	Mirabegron – extended release	25 and 50 mg tablets	June 28, 2012

2.3 Availability of Proposed Active Ingredient in the United States

Oxybutynin chloride has been available in the U.S. since 1975. Since that time, several alternative formulations have been approved. None of the formulations have been removed from marketing due to safety, efficacy or regulatory concerns. See **Section 8 Postmarket Experience** for descriptions of Tracked Safety Issues and subsequent major labeling changes proposed for antimuscarinic drug products indicated for treatment of OAB symptoms.

2.4 Important Safety Issues With Consideration to Related Drugs

See discussion of **Tracked Safety Issues** in **Section 8 Postmarket Experience**.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In 1996, the original IND (#50489) was opened by Theratech, Inc. for oxybutynin in a transdermal patch formulation. The IND was transferred to Watson Pharmaceuticals in 1999. In 2001, Watson submitted data to support filing of NDA 21-351 which required two review cycles and was approved in 2003. Schering-Plough partnered with Watson in 2007 to pursue a switch to OTC marketing status. **Table 2** identifies the key agreements from milestone meetings.

Table 2: Important Meetings and Results During Development of Oxytrol for Women®

Meeting type	Date	Key agreements/points*
Pre-IND meeting	April 16, 2007	Progress on OTC label and LCS proposal
End-of-phase 2 meeting	October 13, 2009	<ul style="list-style-type: none"> • AUS recommended • Co-packaged urine dipstick suggested • Submit study protocols for review
Pre-NDA meeting	September 12, 2011	<ul style="list-style-type: none"> • To provide mitigation analysis criteria • AUS: Provide several additional analyses • Postmarketing safety topics: falls, confusion, disorientation • Safety data will be provided from transdermal formulation only

*See text in this section for details of key agreements/points from pertinent meetings regarding development of Oxytrol for Women®. LCS = label comprehension study

Dr. Steven Osborne reviewed (April 20, 2007) the original pre-IND submission (IND 74288) in 2007 to support a switch to OTC status. There, the sponsor* proposed label comprehension studies (LCS), self-selection (SSS) and actual use (AUS) to support marketing a drug with an indication novel to the OTC marketplace. No additional safety or efficacy trials were proposed. Results from such studies would show that consumers could understand a drug label, select to use the drug appropriately and then use the drug properly and safely in an OTC setting. At that time, the sponsor proposed (b) (4)

FDA also expressed concern that serious conditions may produce OAB symptoms, and that such conditions may not be recognized by consumers. Diagnoses by healthcare professionals may be missed or delayed, worsening the risks associated with OTC availability. Regarding the consumer behavior studies, the following parameters were discussed as the LCS and SSS evolved (The AUS is discussed in **Section 6 Review of Efficacy**):

Label Comprehension Studies

- The label to be tested must be in the “Drug Facts” format and include required content as per 21 CFR 201.66(c) & (d).
- All pertinent warnings and contraindications must be transferred to the OTC label, and must be written in consumer-friendly language.
- Only a well-understood and adequate label should be tested in subsequent self-selection and actual use trials. Production of an adequate label is an iterative process.

* In this section, the designation “sponsor” is a reference to the NDA holder, pre-NDA submission.

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- Nonpharmacologic therapies to manage OAB symptoms should be described and understood by consumers.
- The appropriate target population and “Stop use” criteria should be considered as the sponsor determines a duration of use, short or long term.

Reviewer’s comments: OTC drugs are usually marketed to treat symptoms of limited duration [REDACTED] OAB can be a chronic, long-term condition; however, drug utilization data indicates that use of Oxytrol is often limited to 1-2 months per treatment episode (see below). The benefit-to-risk profile of the drug in the OTC setting was addressed with consideration of all information, including input from an Advisory Committee Meeting.

FDA had several comments and recommendations for a proposed LCS. They were communicated in July 18, 2007. Important recommendations for the LCS instructed the sponsor to

- Determine, a priori, target comprehension levels and minimally acceptable levels.
- Base the sample size on the comprehension rate, the percentage of participants meeting the target comprehension level.
- Consider comparing different iterations of the proposed label.
- Address significant warnings and contraindications that were missing from the proposed label. The label for testing should be revised.

On October 4, 2007, the sponsor responded with revisions of the LCS protocol and labeling. Several of the sponsor’s listed communication objectives in the proposed LCS were considered primary objectives by FDA, not secondary as originally classified. At that time, the sponsor chose to target female consumers for OTC marketing. However, FDA recommended that cohorts of men should be tested to evaluate selection decisions.

FDA met with the sponsor on October 13, 2009 to further discuss drug development. At that time, FDA recommended that the sponsor consider co-packaging a urine dipstick to allow consumers to detect the presence of glucose, white blood cells or blood to aid in diagnosis of serious medical conditions, diabetes, urinary tract infection or other genitourinary disease, for example. FDA made recommendations to include a package insert and other labeling to instruct consumers how to use the dipstick and interpret its results. Such information would need to be tested for consumer understanding and compliance prior to making a self-selection decision whether to use the product. The sponsor expressed concern about proper use and interpretation and whether the rate of detecting common substances, such as microscopic blood in women would prompt unnecessary medical evaluations.

Self-selection Studies

- A medical examination by an experienced healthcare professional to confirm the diagnosis of idiopathic OAB is necessary. The exam should include medical history,

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physical exam with pelvic examination (females) and rectal examination (males) and laboratory assessment including urinalysis and Prostate Specific Antigen (PSA) level, if indicated.

- The sponsor proposed pilot studies to better understand self-diagnosis behavior prior to evaluating behavior in an appropriate target population.

Reviewer's comments: Comments from July 18, 2007 addressed the proposed SSS.

- *Determine, a priori, a target correct self-selection level and minimally acceptable level.*
- *Base the sample size on the self-selection rate.*
- *Target an appropriate population to improve the safety margin, i.e., risk for serious underlying conditions such as prostate cancer, if consumers make self-selection errors, e.g., market only to women or market to a defined age group and direct older consumers to "ask a doctor before use."*

Actual Use Study

There were several discussions and communications between FDA and the applicant to serially amend the AUS. Overall, the applicant amended the protocol seven times, the last time in January 2011. Three administrative changes were made up to January 2011.

Comments from pre-submission meetings on April 16, 2007, July 7, 2009, October 13, 2009, and a July 18, 2007 letter included several specific and general recommendations for a formal trial of actual use in an OTC setting. Most notably:

- Narrow the primary and secondary objectives.
- Establish specified clinical endpoints and justification for proposed sample size.
- Consider co-packaging a urine dipstick to aid identification of serious undiagnosed medical conditions such as UTI, diabetes and urogenital pathology.
- Data should show that pregnant women with urinary frequency first speak with their medical provider, and do not use the drug.
 - Too many pregnant women in early studies chose to use the drug without having spoken to their doctors.
- Ensure that men do not use the drug.
 - In an early study, too many men (15%) still chose to use the drug even though they understood that it was not indicated for them.

The sponsor submitted the AUS protocol (CL2008-13) in January 2010, to open the IND (#74288). The trial was allowed to proceed from a safety perspective, but the FDA had several labeling and design recommendations (see Advice Letter March 23, 2010). FDA suggested that the study design include a primary endpoint to determine the proportion of subjects who did not stop use with new or worsening symptoms, or if there was no improvement in OAB symptoms after two weeks. This is the total number of subjects who meet these criteria divided by the total number of subjects who received at

least one dose of the test drug. FDA recommended that the target error rate be no greater than 5%.

The sponsor submitted several protocol and labeling revisions, but did not agree to the FDA's proposed primary endpoint. FDA offered additional advice (November 15, 2010; April 1, 2011; October 6, 2011):

- FDA did not agree with exclusion of analysis of subjects whose symptoms did not improve after two weeks of use of the drug. Also, the primary endpoint assessment should capture subjects with complaints of abdominal and pelvic pain.
 - The sponsor attempted to justify the exclusion by stating that many subjects were unlikely to respond to the drug within such a short time frame, stating that it may take 4-6 weeks before subjects notice improvement.
- FDA did not agree with the applicant's proposed risk categories based on hierarchy of clinical significance. Some conditions require medical evaluation. FDA advised that these categories would not be considered.

The sponsor considered the appropriateness of the proposed 3.9 mg/day dose. While more AEs were reported at this dose in clinical trials to support original approval (b) (4), and the usual AEs, e.g. skin reactions, and symptoms of anticholinergic reactions, constipation, flushing, vision changes and neurological changes could be included in labeling. See **Section 7.3.5 Submission Specific Primary Safety Concerns**.

2.6 Other Relevant Background Information

Oxybutynin transdermal patches providing 3.9 mg/day are marketed as Rx drugs in several foreign countries including Australia, New Zealand, Canada, and countries in the European Union. The applicant states that the drug has not been withdrawn from marketing for any reason. I compared foreign labels with current and proposed labeling to help determine whether there are additional warnings, precautions or contraindications that should be considered for translation into an appropriate Drug Facts OTC label. Label information that could impact safe use in the OTC environment, but not listed in proposed labeling includes only:

- Warnings that symptoms of hyperthyroidism, coronary heart disease, CHF, arrhythmias, tachycardia, and hypertension may be worsened.

*Reviewer's comments: Also see **Section 9.2 Labeling Recommendations**.*

Evaluation of Observational Study (CL2010-08)

In 2010, the applicant conducted a multi-centered, retrospective electronic health record review entitled "Characterizing the Incidence of Initial Presentation of Urinary Frequency in Women Diagnosed with Urinary Tract Infection, Diabetes Mellitus or Bladder Cancer." The objective was to evaluate the incidence of UTI, diabetes or bladder cancer in

female patients 18-85 years of age who presented to their physicians with initial primary complaints consistent with symptoms of OAB. The applicant conducted the study to support the appropriateness of an OTC drug treatment for OAB. The primary endpoint was the binomial presence/absence of a primary complaint scored “Yes” for OAB symptoms, two or more of urinary urgency, frequency or urge incontinence when the final diagnosis was UTI, diabetes, or bladder cancer.

Records were identified by ICD-9 diagnostic codes, and were further screened through additional criteria. Nearly 1600 records were identified and available for analysis. There were 706 UTI records, 609 diabetes records, and 284 bladder cancer records. Two physicians (a urologist and a family medicine physician) independently reviewed the records and decided whether presenting symptoms reflected OAB. The investigator determined inter-rater agreement by the Kappa test (agreement is $Kappa \geq 0.8$) to assess the raters’ scoring. Both OAB and non-OAB symptoms were scored by the raters. The estimated proportion of subjects presenting with OAB symptoms, based on sample sizes for each cohort (UTI, diabetes, bladder cancer), was < 5% with UTI and diabetes, and 5-10% with bladder cancer.

Point prevalence of OAB in each group:

- UTI – 2.83% (20/706) with 95% CI 1.78%, 4.41%
- Diabetes – 1.48% (9/609) with 95% CI 0.72%, 2.89%
- Bladder cancer – 7.39% (21/284) with 95% CI 4.75%, 11.24%

Reviewer’s comments: Ultimately, rater agreement was adequate. Re-scoring was required for both the diabetes and bladder cancer cohorts. It is not clear how the investigator determined, from the structure of the “presenting complaint,” the patients’ primary concerns. Often, several different complaints were recorded in the chart, and it is not clear how they were prioritized. It is not clear why there was initial disagreement on complaints in the diabetes and bladder cancer cohorts. The initial prevalence rates were 6.4% in the diabetes cohort, and 9.2% in the bladder cancer cohort.

Patients with UTI most frequently presented with back/flank/abdominal pain (33%), dysuria (28%) and general malaise, fatigue or pain (17%). More patients over age 40 than under age 40 reported OAB symptoms (3.9% vs. 1.6%). Patients in the diabetes group most frequently presented for simple follow-up visits or routine lab tests (49%). One quarter reported a high glucose reading from a borrowed home blood glucose meter. Non-OAB symptoms of these diabetes patients were most frequently pain (19%) and general malaise/fatigue (16%). In the bladder cancer group, the most common presenting symptom was hematuria (49%). Frequently reported non-OAB symptoms included follow-up for routine labs (29%), pain (18%), and dysuria (12%). UTI appears to be most often symptom-driven in the study population, meaning that pain or dysuria is frequently experienced. Such symptoms are not part of the symptom complex of OAB. The results also show that diabetes diagnoses are more often the result of routine care and patients are frequently asymptomatic for extended periods of time prior

to diagnosis. Bladder cancer may resemble both UTI and OAB in some ways, but hematuria is a better indicator of more serious medical conditions, and the proposed label includes warnings against use if consumers have hematuria.

Reviewer's comments: This study is not pivotal to approval of this application. A brief review of the results is provided here to help assess how frequently OAB symptoms are present when serious medical conditions are subsequently diagnosed. The results reveal that small numbers of patients presented to their physicians with OAB symptoms due to UTI, diabetes or bladder cancer. Many patients who were subsequently diagnosed with diabetes and bladder cancer presented to their doctors for simple lab and visit follow up appointments.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality of the submission was adequate. It was reasonably well-organized and the DVD review aid included working hyperlinks and improved the ease of review. The original submission contained the vast majority of information to allow evaluation and review. At our request, the applicant submitted a line listing for subjects who misused the drug based upon Secondary Endpoint 5 – Proportion who misused based on extended duration of use (> 4 days) or simultaneous use of more than one patch. They submitted a revised listing because some mitigation decisions were changed, and submitted tables of misuse by simultaneous use only, separated by age for subgroup analysis. FDA had a teleconference with the sponsor in September 2012 to discuss the mitigation decisions for these subjects. The sponsor described how the decisions were made. At several points during the review, the sponsor submitted case report forms (CRFs) at FDA's request. They submitted clinical and nonclinical data to support their contention that dermal carcinogenicity data is unnecessary. The applicant submitted a timely and pertinent 120-day safety update. The applicant submitted additional, clinically relevant responses to requests for information throughout the review period.

3.2 Compliance with Good Clinical Practices

The central Institutional Review Board (IRB), [REDACTED] (b) (4) [REDACTED] approved the protocol, advertising and recruitment materials, Informed Consents and all pharmacy sites for the Actual Use Study. The applicant asserts that all study procedures complied with Good Clinical Practice Guidelines and principles under the Declaration of Helsinki, as well as applicable laws and regulations. The final versions of the Informed Consent (January 14, 2011) form and AE reporting forms were adequate and without biases.

Reviewer's comments: The Informed Consent for users describes certain potential risks including skin reactions and typical anticholinergic effects. For the most part, the important risks are included in proposed labeling. Notably, the Consent describes risk for heat stroke due to decreased sweating. See Section 9.2 Labeling Recommendations for further comment.

In the AUS, there were 95 protocol deviations by 91 subjects. Eight six (86) were users. Over 70% were due to errors in Informed Consent gathering. The remainder was mostly for administrative reasons. There were no associated safety issues.

We requested an audit of the AUS by the Office of Scientific Investigations (OSI). We identified three pharmacy sites and the headquarters of the Contract Research Organization (CRO), (b) (4) for inspection. Two sites, Stevenson Family Pharmacy (St. Joseph, MO) and Matt's Medicine Store (Independence, MO) were selected because they were the highest enrollers and had the highest number of discontinuations from the trial. The latter pharmacy also reported the highest number of serious AEs (n=7). The third site, Catonsville Pharmacy (Baltimore, MD) had the highest number of discontinuations as a percentage of those enrolled (27%). This site enrolled 26 subjects and also reported two serious AEs, including the single death in the trial. Each site reported several protocol deviations where out-of-date Informed Consent forms were used. (b) (4) maintains the trial master files and source data. OSI reported that all site inspections were completed by the end of July 2012.

The final reports on two study sites and the CRO did not identify any issues (finalized 11/2/12; DARRTS). All study records for enrolled subjects were adequate, and there were no violations. One site, site #12 in Independence, MO, did not completely adhere to the protocol. Specifically, urinalyses were not performed at the end of the trial for 13 of 52 subjects as per protocol and urinalysis test strips failed Quality Control testing. OSI did not believe these minor violations increased risk to the subjects, or impacted the integrity of the data. This reviewer agrees.

3.3 Financial Disclosures

There do not appear to be any financial relationships between the applicant and the study sites or CRO that would impact the conduct or results of the clinical trials submitted with this application to support approval. An applicant-completed FDA Form 3454 was submitted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no differences in the Rx or proposed OTC versions of the drug product. The drug substance, oxybutynin, is a racemate of R- and S-isomers. In the transdermal formulation, the drug is part of a matrix-type system with three layers. The first layer is a thin, flexible backing film acting as an occlusive and helping to maintain patch integrity. The second layer is the adhesive/drug layer containing oxybutynin and triacetin, (b) (4). The third layer is a release liner peeled off and discarded in order to apply the product to skin. Individual patches are packed in heat sealed, tear-resistant pouches.

Side View

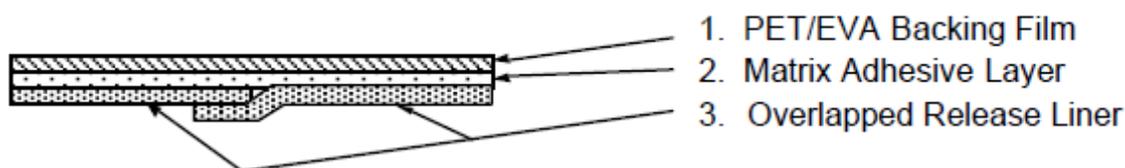


Figure 1: Side View of Oxytrol for Women® (PET/EVA – polyester/ethylene-vinyl acetate; see Module 3.2.P.1)

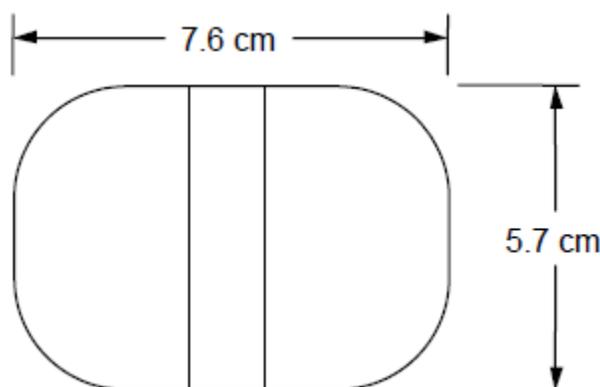


Figure 2: Top View of Oxytrol for Women® (see Module 3.2.P.1)

On July 27 and August 24, 2012, at FDA's request, the applicant submitted an assessment of quality-related reports or complaints, reports of medication errors, or reports of adhesion issues submitted to the NDA holder related to issues of excessive (b) (4). Excessive (b) (4) affects removal of the patch from its container closure, or pouch. Essentially, the patch becomes stuck to the interior of the closure and affects usability in any setting, Rx or OTC. We had requested reports for the currently marketed product as well as from subjects in the CONTROL trial. We requested lot trends as well.

The applicant stated that there were no related reports stemming from the CONTROL trial. Only a single lot was used in the trial. Out of 8850 total patches used in the trial,

659 (7.4%) reportedly fell off. Nearly 37% of subjects in the trial reported at least one patch falling off. Over the duration of Rx marketing, adhesive-related quality issues accounted for 0.008% of over 50 million units distributed. Three lots were investigated in 2011 for related issues, and corrections were made. Overall, the applicant reports:

- 202 cases – “Difficult to peel apart,” or difficulty removing the backing from the patch
- 2101 cases – adhesion failure, or problem with patch not sticking
- 1885 cases – adhesive issues, or other issues separate from adhesion failure

The greatest reporting of events occurred between mid-2003 to mid-2004 (0.028%-0.043%), however, the number of cases, overall, is miniscule with regard to the distribution of the product. There were no related medication errors reported.

The applicant has tested, and FDA has inspected, several samples at varying post-manufacture dates, up to 35 months in age. It appears that (b) (4) starts to become an issue by (b) (4). Based on the totality of currently available information, the CMC team will require a 24-month expiry. The applicant is currently requesting a (b) (4). The CMC reviewers have recommended a Complete Response due to unresolved issues of drug product quality.

4.2 Clinical Microbiology

Not indicated.

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical/toxicology data were submitted to support this application. Dr. Cindy Li’s nonclinical review recommends approval (DARRTS, November 9, 2012). According to the approved Rx label, a 24-month rat study at oral dosages up to 160 mg/kg, or 50 times the maximum exposure in humans taking an oral dose, did not show any evidence of carcinogenicity. No dermal carcinogenicity studies of oxybutynin have been done. Additional studies in multiple species revealed no evidence of mutagenicity, impairment of fertility or harmful effects on the fetus.

Typically, externally-applied OTC drugs that are likely to be used chronically over a consumer’s lifetime require support for safety from chronic toxicity and carcinogenicity studies in animals.

Reviewer’s comments: On June 25, 2012, the applicant provided additional information to support dermal safety with chronic use.

The applicant justified the lack of data from studies with the following:

- During development of the original Rx product, FDA commented that data from animal irritation and sensitization studies were sufficient to support safety. Further,

more recent approval of an oxybutynin drug product in a gel formulation did not require chronic toxicity or carcinogenicity studies.

- Structures from *in silico* modeling analysis of oxybutynin and desethyloxybutynin did not resemble any compounds with carcinogenic potential.
- Genotoxicity and nongenotoxicity investigations related to carcinogenicity did not raise concern during the original review of the Rx product. According to the applicant, the skin is not particularly sensitive to nongenotoxic carcinogens.
- The “Report on Carcinogens,” regularly published by the Dept. of HHS to identify known or reasonably anticipated carcinogens, has never included oxybutynin.
- The applicant performed a search of Watson’s pharmacovigilance database in February 2012 for reports listing AEs under the MedDRA System Organ Class (SOC) of “skin and subcutaneous tissue disorders.”

While over [REDACTED] (b) (4) of the drug were distributed worldwide over the nine years since approval, they report that none of the reports uncovered cases related to long term exposure and toxicity with chronic use. There were no reports of skin cancer. They report that no such events have been reported in the published scientific literature or at major urology research conferences.

Additionally, data and concerns were presented to the FDA’s executive Carcinogenicity Assessment Committee (CAC) on September 4, 2012, a body that advises on issues related to carcinogenicity concerns. The Committee addressed whether dermal carcinogenicity studies should be waived for this Rx-to-OTC switch application. If a study can be required of the applicant, it should be a full 2-year study performed pre-approval. Determining whether such a study will be needed may rest on whether the application is truly a 505(b)1 application, i.e., whether it relies completely on studies conducted only by the applicant, or the NDA holder under right of reference. Following further internal discussion, the existing quantity and quality of data relevant to the issue appears adequate to support use in the OTC setting if the drug is approved for OTC use.

- Comparison of data from Watson’s pharmacovigilance database to that described by Friedman, et. al.⁵ supports the safety of oxybutynin in the context of cancer risk.

This group performed exploratory screening of 105 commonly used drugs, including unidentified formulations of oxybutynin, to assess the potential for carcinogenic effects for patients covered by the Kaiser Permanente Medical Care Program of Northern California. Ascertainment of use was based on prescriptions dispensed over the observation period which ended on December 31, 2006, nearly four years after approval of Oxytrol®. The assessment showed a potential association between oxybutynin use

⁵ 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.

and non-melanoma skin cancers including Merkel cell carcinoma, a rare, but highly aggressive primary skin cancer with a high rate of mortality. Of over 110,000 patients who were dispensed the drug, 12 skin cancer cases (Relative Risk=2.34; p value <0.009) were identified. Five reported Merkel cell carcinoma. Average duration of use until time of diagnosis was 18 months. This association met the authors' criteria of Risk Ratio > 1.5 for three or more dispensings in a two year lag analysis, p<0.01 for differences from an RR of 1.00, and RR for three or more dispensings greater than the RR for one dispensing as a crude indication of dose-response. Rates were compared with 10 age-, sex- and membership initiation date-matched controls. Clinical and biological connections were investigated through evaluation of the scientific literature. None were found.

The article did not state whether the subjects who developed Merkel cell carcinoma had used a dermal formulation of oxybutynin. The lead author was contacted and he stated that, while formulation information was not available for specific cases, most prescriptions for oxybutynin during the study interval were for oral oxybutynin products. There were (b) (4) Oxytrol® prescriptions dispensed from 2003 through 2004. In 2003 alone, there were nearly (b) (4) prescriptions for oral oxybutynin products. There were no details on location of cancers or age of patients. The authors did not recommend further evaluation of this particular association, although they did recommend further studies of eight unrelated drugs.

An internal discussion and review of data, regarding the skin cancer findings, between the Director of the Division of Nonprescription Products and the Director of the Division of Dermatology and Dental Products resulted in agreement that the findings did not identify a safety signal, and that no further dermal carcinogenicity studies would be required.

4.4 Clinical Pharmacology

There are no proposed changes to the directions for use that required new clinical pharmacology studies to support this Rx-to-OTC switch application. The OTC directions are within the limits of those approved for the Rx drug product. See Dr. Gierhart's and Dr. Choi's respective reviews for details of the clinical pharmacology portion of the original application.

4.4.1 Mechanism of Action⁶

Oxybutynin is a tertiary amine ester with antimuscarinic and antispasmodic effects on smooth muscle. The antimuscarinic effect is non-selective and may produce

⁶ Clinical Pharmacology Online – oxybutynin (<http://www.clinicalpharmacology-ip.com/Forms/drugoptions.aspx?cpnum=456&n=Oxybutynin>); accessed July 16, 2012, and current, approved labeling for Oxytrol®.

anticholinergic side effects. The antispasmodic component of the drug exerts a significant effect on M1 and M3 muscarinic receptors in bladder detrusor muscle, in competition with acetylcholine. The drug acts as a bladder muscle relaxant, suppressing the urge to void. Without frequent contractions, the bladder may increase both its fill capacity and the volume to first contraction.

4.4.2 Pharmacodynamics

See Dr. Choi's review. Changes in serum concentration appear dose dependent and increase linearly. There are no proposed changes to the dose.

4.4.3 Pharmacokinetics

This section is based on review of the Rx label and clinical pharmacology online³. See Dr. Choi's review as well. Oxybutynin is a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. Its main metabolite, N-desethyloxybutynin (NDEO), is active with similar effect on bladder detrusor activity as oxybutynin. This metabolite is also believed to be the primary causative agent for anticholinergic side effects⁷. The average daily dose, 3.9 mg, is passively absorbed through the skin with transdermal application. Application of the first patch leads to increasing systemic oxybutynin concentrations up to 4 ng/mL at 36-48 hours post-dose. The drug is widely distributed and steady concentrations are maintained for up to 96 hours. Application to the abdomen, buttocks and hips provides the same absorption and concentration levels. Steady state conditions are reached after application of a new, second patch (see **Table 3**).

Table 3: Mean (SD) PK Parameters from Single and Multiple Dose Studies in Healthy Volunteers (1st row – Male; 2nd row – Female)

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

¹ T_{max} given as median

² AUC_{inf}

³ AUC₀₋₉₆

⁴ AUC₀₋₈₄

Source: Pharmacokinetics section of Oxytrol® prescription label.

⁷ Zobrist RH, B Schmid, A Feick, D Quan, SW Sanders, 2001, Pharmacokinetics of the R- and S-Enantiomers of Oxybutynin and N-Desethyloxybutynin Following Oral and Transdermal Administration of the Racemate in Healthy Volunteers, *Pharm Res*, 18: 1029-1034.

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Oxybutynin is mainly metabolized by the CYP3A4 enzyme system. Because CYP3A4 is mostly localized to liver and gut wall, formation of the active metabolite is minimized with transdermal application. The plasma concentration Area Under the Curve (AUC) ratio of active metabolite to parent compound following multiple applications is approximately 1.3:1, which is less than the ratio following oral delivery, 4.1:1. The half-life of oxybutynin after removal of the patch is 7-8 hours. Only 0.1% of the drug is excreted unchanged in the urine. Also, only 0.1% is excreted as active metabolite. There do not appear to be any major PK differences based on age, gender or race. Pediatric use and use in patients with renal or hepatic insufficiency were not evaluated.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4: Consumer Behavior Studies and Trials Supporting NDA 202211

Study Type	Objective	Design/Control group	Test product/ Dosage regimen	Subjects	Study size	Duration
AUS (CL2008-13)*	Post-purchase behavior and actual use in OTC setting	- Recruit/enroll all comers from 26 retail pharmacy sites. - No control group	Oxytrol for Women® patch used as per understanding of proposed label.	Females 18 or older	785 total users	12 week use period; 15 week total duration
RECR (CL2010-08)*	Determine incidence of females (18-85 y) with UTI, DM or bladder cancer who presented to doctor with primary complaints of OAB	Four site retrospective electronic medical record analysis study	None	Female patients' records identified through ICD-9 codes for UTI, DM, bladder cancer	1599 subjects	N/A
LCS (82023)	- Comprehension of label for use, directions and warnings in three general female populations - Evaluate male comprehension that product is for women	- Recruit/enroll from 16 market research sites. Done via databases or mall-intercept. - No control group	None	Four cohorts: - Literate females >18 (n=196) - Low lit. females >18 (n=204) - Gen. population females without OAB symptoms >18 (n=199) - Gen. population males >18 (n=76)	675 subjects - First two cohorts had OAB symptoms	One site visit

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Study Type	Objective	Design/Control group	Test product/ Dosage regimen	Subjects	Study size	Duration
LCS (92062)	Comprehension of precaution to speak with a physician if woman of childbearing age may be pregnant	Recruit/enroll from nine market research sites	None	Two cohorts: - Gen. population females 18-40 yrs (n=350) - Augmented low lit. 18-40 yrs (n=224); Total low lit.(n=252)	574 healthy subjects	One site visit
LCS (92099)	Comprehension of label components describing undiagnosed DM	Recruit/enroll from nine market research sites	None	Two cohorts: - Gen. population females >18 (n=360) - Augmented low lit. >18 (n=230); Total low lit. (n=258)	590 subjects – All had OAB	One site visit
LCS (92101)	Comprehension of label components among women >65	Recruit/enroll from seven market research sites	None	Women over age 65	350 subjects - All had OAB	One site visit
LCS (10053) [∞]	- Comprehension of label for use, directions and warnings in two general female populations - Comprehension of label components describing undiagnosed DM among subjects with DM risk	Recruit/enroll from nine market research sites	None	Three cohorts: - Gen. population females >18 (n=472) - Augmented low lit. >18 (n=120); Total low lit. (n=152) - Females >44 with some DM risk (n=160)	752 subjects - 1 st /2 nd cohort had OAB	One site visit
SSS (CL2009-07) [^]	Determine deselection behavior of women with contraindicated urinary symptoms	- All female comers at seven clinics in the U.S. - No control group	None	Females with urinary urgency or frequency and(≥ 1): Pain/burning; lower back/side pain; cloudy/foul smell; blood in urine	105 subjects	One interview

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Study Type	Objective	Design/Control group	Test product/ Dosage regimen	Subjects	Study size	Duration
SSS (CL2008-19)	- Evaluate self-diagnosis of OAB - Evaluate self-selection based on medical history and label understanding.	- Recruit/enroll by ads, outreach and databases at eight clinics - 1 st /2 nd cohorts examined by physicians to confirm diagnosis	None	Three cohorts: - Literate females >18 (n=218) - Low lit. females >18 (n=137) - Mixed >18 (males (n=172); diabetic (n=42); glaucoma (n=12); pregnant/nursing (n=10))	587 subjects - All had OAB - Cohort 3 had ≥1 contraindicated condition	One site visit unless subject postponed medical exam
SSS (92061)	Determine deselection behavior of men who are not to use the product.	Recruit/enroll from nine market research sites - No control group	None	Two cohorts: - Gen. population of men >18 (n=354) - Total low lit. (n=273) - Augmented low lit. men >18 (n=217)	571 subjects - All had OAB	One site visit
SSS (10054)	Determine selection behavior of pregnant women - Should speak to physician first	Recruit/enroll from nine market research sites - No control group	None	Two cohorts: - Gen. population of pregnant women (n=308) - Augmented low lit. pregnant women (n=127); total low lit. (n=142)	435 subjects - All pregnant women had OAB	One site visit

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Study Type	Objective	Design/Control group	Test product/ Dosage regimen	Subjects	Study size	Duration
Quality of Life (QoL) study (OXY0402 – MATRIX)	Evaluate QoL changes and tolerability over six months of Oxytrol® use in the Rx setting.	Recruit/enroll from 327 community health sites -Compare subjects using Oxytrol® plus behavioral intervention-enhanced patient education (BIEPE) versus Oxytrol® plus ordinary care (OC)	Oxytrol® as prescribed	Comparison groups - BIEPE (n=1598) - OC (n=1283) Subjects were treatment naïve, previously on therapy, or currently unsatisfied with OAB treatment	2881 male and female subjects - All had OAB	Four site visits and up to six monthly phone interviews

Source: Adapted from Applicant’s Module 5.2 Tabular Listing of all Clinical Studies, and from other described clinical studies/trials in the application.

* This review will focus on the Actual Use Study (AUS) and Retrospective Electronic Chart Review (RECR). See Ms. Barbara Cohen’s review for analysis of the Label Comprehension Studies (LCS) and Self-selection Studies (SSS).

^ Study terminated early due to potential biases based on feedback from FDA.

∞ Pivotal LCS.

Table 5: Clinical Efficacy, Skin Safety and Pharmacology Trials Supporting NDA 21351

Study Type	Objective/ 1° Endpoint	Design/Control group	Test products/ Regimen	Subjects	Study size	Duration
Efficacy (O96017)	Dose ranging, efficacy and safety % responders after 4 weeks (30% reduction in daily episodes)	Randomized, double blind, parallel Oral oxybutynin tablet: control	Transdermal oxybutynin (1, 2, 3 (39 cm ²) or 4 patches) twice weekly Oral tablet (2.5mg BID, 5 mg BID, 5 mg TID, 7.5 mg TID)	92% female; average age 63.5 years Have urge incontinence with bladder instability or hyperreflexia and improvement w/ oral oxybutynin	12 locations (72 completers): Oxybutynin tablet (n=35) Oxytrol® (n=37)	6 weeks
Efficacy (O99009)	Efficacy and safety Reduced number of episodes per week compared to placebo group	Randomized, double blind, parallel Placebo: control	Transdermal oxybutynin (13, 26, 39 cm ² patches) twice weekly Placebo patch (13 or 26 cm ²)	91% female; average age 61.4 years Have OAB symptoms: urge incontinence, urgency, frequency	40 locations (447 completers) Avg. 108 in test groups; 122 in placebo group	12 weeks
		Open-label extension	Transdermal oxybutynin twice weekly		199 in 39 cm ² group; others-159	12 weeks
Efficacy (O00011)	Efficacy and safety Change in mean episodes	Randomized, double blind, parallel Tolterodine and placebo comparators	Transdermal oxybutynin 39 cm ² patch twice weekly Tolterodine LA 4 mg capsule once daily Placebo patch 39 cm ² twice weekly	93% female; average age 63 years Have OAB symptoms: urge incontinence, urgency, frequency responsive to current treatment	48 locations (320 completers) 97 in test group; 116 in tolterodine group; 107 in placebo	12 weeks
Study Type	Treatment		Duration		Subjects	
Single dose PK, 2-way crossover (O96003)	1) 10 cm ² transdermal system 2) oxybutynin 5 mg tablet		1) 96 hours 2) single tablet		N=15 (53% female)	

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Study Type	Treatment	Duration	Subjects
Skin irritation and cumulative irritation	1) 5 cm ² transdermal system 2) Placebo transdermal system	One test drug and one placebo applied daily for two weeks	N=29 (52% female)
Skin irritation and sensitization	1) 5 cm ² transdermal system 2) Placebo transdermal system	One test drug and one placebo applied three times weekly (3 weeks); 24 hour exposure with application	N=115 (63% female)
Single dose PK, 2-way crossover (O99005)	1) 39 cm ² transdermal system 2) oxybutynin 5 mg tablet	1) 96 hours 2) single tablet	N=18 (56% female)
Single dose PK, 3-way crossover (O99006)	39 cm ² transdermal system on: 1) abdomen 2) buttock 3) hip	96 hours with seven day washout in between use	N=24 (54% female)
Multidose PK, 3-way crossover (O99007)	1) 13 cm ² transdermal system 2) 26 cm ² transdermal system 3) 39 cm ² transdermal system	Each arm: Two patches x 84 hours; one patch x 96 hours with 14 day washout in between use	N=26 (50% female)

Source: Adapted from Table 1, Module 2, Section 2.7.3, p. 7 of applicant's submission and from Dr. Brenda Gierhart's review

5.2 Review Strategy

Section 6 Review of Efficacy and **Section 7 Review of Safety** include discussion of the AUS, CONTROL. Safety in the CONTROL trial includes assessment of the reported adverse events in total, and by category of pertinent safety topics of interest (see **Section 7.3.5 Submission Specific Primary Safety Concerns**). Efficacy evaluation includes assessment of generalizable effectiveness in the naturalistic, OTC setting, that is, how well subjects appeared to understand and follow the label, and how they used the product at home. I assessed labeling evaluation, purchase decisions, use and misuse as determined by several pertinent endpoints, and the safety data from the trial.

See Barbara Cohen's review, from the social science perspective, for further details on the LCSs and SSSs. In addition to the AUS, this reviewer also considered:

- Data submitted to support approval of the original Oxytrol® drug product, under NDA 21351
 - Drug utilization data (see **Section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**)
- The clinical implications of nonclinical data (see **Section 4.3 Preclinical Pharmacology/Toxicology**)
- The clinical implications of findings related to chemistry, manufacturing and controls (see **Section 4.1 Chemistry Manufacturing and Controls**)
- The postmarketing experience (see **Section 8 Postmarket Experience**) of Oxytrol® since its original approval in 2003. Postmarketing experience includes
 - Data from various worldwide safety databases, including the NDA holder's database
 - The applicant's retrospective, observational, health records' study (CL2010-08) to determine incidence rates of several diagnoses with symptoms similar to OAB
 - Uncontrolled safety data from the NDA holder's MATRIX trial conducted to evaluate Rx use, tolerability and quality of life in a "naturalistic" setting
- Published scientific literature
- Proposed Drug Facts labeling

5.3 Discussion of Individual Studies/Clinical Trials

See **Section 6**.

6 Review of Efficacy

Efficacy Summary

The applicant submitted several consumer behavior studies to support safe and proper use of the product in the OTC setting. The LCSs and SSSs will be reviewed by Barbara Cohen, Social Science Analyst in DNCE. I will review the CONTROL trial, evaluating use and misuse in the OTC setting. I will present the data for how well subjects appeared to understand and follow the label, and how they used the product at home.

For efficacy, the applicant relies on results of trials submitted to support the original NDA for prescription use. See Dr. Gierhart's and Dr. Batra's reviews. Assessment of efficacy in controlled clinical trials was based on a decrease in the number of urinary incontinence episodes, frequency of daily micturition, and void volume. Oxybutynin in this transdermal formulation has been shown to be efficacious by these measures. Efficacy trial data supported median treatment effects of four less episodes of incontinence per week, two less episodes of daily frequency, and an increase of around 25 mLs of urine per void. Efficacy was not further assessed in the AUS.

Overall, the design and conduct of the CONTROL trial were adequate and typical of AUS. The study population adequately reflected the U.S. population and included an enriched population of older subjects > 65 years of age and > 75. **Table 6** shows the point estimates of the misuse rates by the major endpoints. These endpoints were acceptable. There was a total of five secondary endpoints, three of which (1, 2 and 4) did not materially affect my analysis of use and misuse. The primary endpoint was the proportion of users of at least one patch who did not stop use after reporting new or worsening symptoms identified in the label, or abdominal or pelvic pain. **The a priori threshold misuse rate was $\geq 5\%$, and the applicant met the threshold.** The upper limit of the 95% confidence interval for misuse by the primary endpoint was 5% for all users. The secondary endpoint 3 (SE3) was the proportion of users who used the drug for two weeks, completed the week 3 interview and who did not stop use after reporting no improvement or worsening of their OAB symptoms. The secondary endpoint 5 (SE5) was the proportion of users of at least one patch who misused by using the drug for longer than directed (> 4 days) or using multiple patches simultaneously. All three endpoints were mitigated. See **Sections 6.1.4 Analysis of Primary Endpoint** and **6.1.5 Analysis of Secondary Endpoints(s)** for details and comments on the analysis of misuse and the mitigation strategies.

The applicant also performed an exploratory, post-hoc analysis of misuse by the primary endpoint to evaluate the degree of incorrect use. They determined the proportion of users who reported pertinent symptoms and did not stop use from all users who reported pertinent symptoms. Here, the post-mitigation misuse rate was 17.7% compared to the primary endpoint point estimate of 3.4%. This higher rate may be more clinically relevant, but it must be interpreted with caution since the trial was not

powered to analyze this rate. It would be very difficult to predict during the design of the trial how many users will experience and report pertinent symptoms in order to assess misuse. This reviewer calculated a similar exploratory, post-hoc analysis of misuse by SE3. I evaluated the proportion of users who misused out of only those who used the drug for two weeks, and reported no improvement or worsening of OAB symptoms. This rate appears more clinically relevant, but must also be interpreted with caution. Misuse of the drug by these endpoints can not be evaluated on its own. See **Section 7 Review of Safety** for evaluation of misuse in the context of safety.

Table 6: Summary of Misuse Rates by Major Endpoints (CONTROL)

Endpoints	Misuse – Pre-mitigation	Misuse – Post-mitigation
Primary Endpoint		
User had new or worsening symptoms, and failed to stop use/all users of at least one patch	14.4%	3.4%*
Same user who failed to stop use/all users with pertinent symptoms**	74.5%	17.7%
Secondary Endpoint 3		
User had no improvement or worsening and failed to stop use/all users of 2 weeks of drug	22.6%	11%
Same user who failed to stop use/all users of 2 weeks with no improvement or worsening**	77.5%	38%
Secondary Endpoint 5		
Incorrect user (too long or too many TDSs)/all users of at least one patch	51%	21%

** These misuse rates were exploratory, post-hoc, subgroup analyses

* *a priori* threshold ≤ 5%

Oxytrol for Women® is a novel drug considered for introduction to the OTC marketplace. Its approval would meet a medical need for increased access for women who suffer from OAB. Adequacy of the proposed OTC indication (**Section 6.1**) is addressed more fully in **Section 7 Review of Safety** because the indication attempts to exclude consumers who may have other, more serious medical conditions, and **Section 7** addresses whether diagnosis of these conditions may be delayed with use of Oxytrol for Women®.

6.1 Indication

The proposed OTC indication is “treats overactive bladder in women.” Further, “you may be suffering from overactive bladder if you have had 2 or more of the following symptoms for at least 3 months:

- Urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours)
- Urinary urgency (a strong need to urinate right away)
- Urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate)

The prescription indication is "...treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." See **Section 9.2 Labeling Recommendations** for comments on the indication.

6.1.1 Methods

The AUS is titled the Consumer Trial of Qxytrol (CONTROL; CL2008-13). This was a phase 3, multicentered, open-label, consumer behavior trial open to all comers to assess use of the proposed drug in a simulated OTC setting. Initial enrollment to completion of the trial lasted from May 2010 – June 2011. The trial report was finalized on February 22, 2012. Twenty six pharmacies throughout the U.S. participated in enrolling subjects and conducting the trial.

CONTROL was a four phase trial:

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

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

Recruitment advertising was established to attract women concerned about their OAB symptoms. See **Figure 3** for details of the enrollment process. Screening criteria required that subjects were:

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

Reviewer's comments: Male consumers were not targeted via recruitment materials. The applicant clearly attempted to get only the attention of women. The words "Attention Women" are at the top of flyers which include a silhouette of a women and other photos of women. The flyers are pink. Males who did respond to these materials were excluded from the enrollment and use phases. While the applicant stated that men's reasons for inquiring about participation would be gathered, inquiries were not made.

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Once at the pharmacy site, subjects were asked to view the package and make their own purchase decision. There was no self-selection component of the trial because multiple SSSs had already been conducted, and the applicant wished to maintain as naturalistic a setting as possible from recruitment through the end of study. Following a decision to purchase, subjects responded to enrollment interview questions about their OAB symptoms, medical history and demographics. Subjects who reported either of the following urinary symptoms were excluded from entering the use phase and referred to a physician for evaluation:

- blood in the urine not related to menses
- back pain and fever with OAB symptoms and any of the following:
 - dysuria
 - hematuria
 - cloudy urine

Reviewer's comments: Subjects were not necessarily excluded from using the product if they reported other proposed "Do not use" symptoms on the Drug Facts label such as isolated dysuria, unexplained lower back or side pain, cloudy or foul-smelling urine, or stress incontinence.

Then subjects completed the validated Rapid Estimate of Adult Literacy in Medicine (REALM) test (cutoff < 61 for low literacy) and were assessed whether they met additional exclusion criteria (narrow angle glaucoma, pregnant or breastfeeding or known allergy to oxybutynin). Regardless whether they met criteria, all subjects reported their reasons for purchase decisions. Subjects who signed the Informed Consent, and were not excluded, were invited to enter the use phase of the trial. All subjects, including excluded subjects who had selected to purchase the drug, were asked to provide further Informed Consent to conduct follow up telephone interviews and obtain medical records from any physician visits.

Subjects who purchased the product used it as they understood the Drug Facts label. A diary and follow up interviews at 3, 7 and 12 weeks after initial purchase were used to record patterns of use (a random sample of 10% of interviews were monitored). "Verified users" were subjects who used at least one patch, indicated in the diary returned to the study coordinator, and had at least one follow up interview. These were the users evaluated in the applicant's primary endpoint. "Non verifiable users" were subjects who reported using the drug at a follow up interview but who did not return a diary, or who returned a diary indicating use but who did not complete at least one follow up interview. Subjects were provided contact with a healthcare professional 24 hours per day for the trial duration. Subjects could purchase up to 24 packages of Oxytrol for Women® over the duration of the trial.

Reviewer's comments: The applicant proposes draft packages, for marketing upon approval, that contain 4, 10 or 14 patches per package, to be used for 16, 40 or 56 days of treatment, respectively. Only the 4-count package was available for purchase in the

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AUS. Therefore, a subject who used the patch daily over the 12-week use period needed to purchase at least 6 packages. Although FDA recommended (letter; March 3, 2010) that the applicant offer subjects packages with the largest number of patches proposed for marketing, allowing purchase of up to 24 boxes should allow for adequate assessment of misuse and overuse by unlabeled co-administration of multiple patches.

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

Reviewer's comments: Two procedural changes were undertaken after enrollment began. On July 14, 2010, the purchase price of the drug was decreased from \$10 to \$5, and the introduction script, when subjects were handed the Drug Facts label, was lengthened. These changes did not appear to impact subjects' purchase decisions.

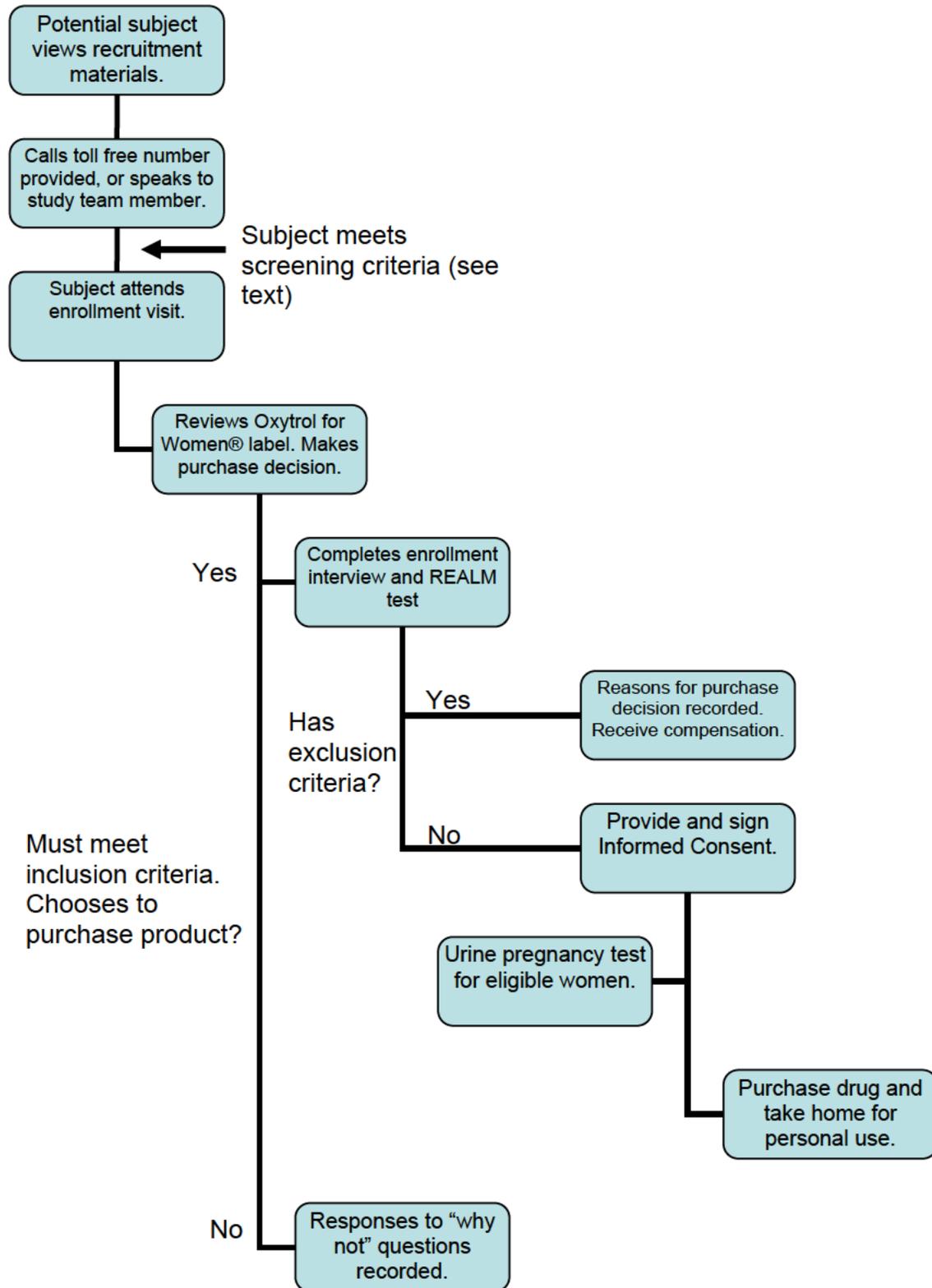


Figure 3: CONTROL Trial Enrollment Diagram

6.1.2 Demographics

As shown in **Table 7**, non-white subjects accounted for nearly 23% of the verified user population. Age was widely distributed, 18-94, with adequate means and medians for label evaluators (57.9, 58) and purchasers (58.4, 58). Subjects over age 65 years, and over age 75 years, accounted for 32.7% and 16.6% of the verified user population, respectively. 2011 U.S. census data⁸ indicates that non-whites (including Hispanic persons) make up nearly 37% of the population, and just over 13% of the U.S. population is ≥ 65 years of age. Further, the applicant selected four of the 26 pharmacy trial sites based on their high percentage of customers > 65 years of age. These sites were contracted to increase enrollment of older subjects for further subgroup analysis. The elderly population, a key marketing demographic if the product is approved, is well-represented in the trial. Over 92% of subjects who evaluated the label were high school graduates, or had an equivalent degree. Of note, 162 (13.3%) of the label evaluators were determined to be low literate.

Reviewer's comments: The race, age, education and literacy subpopulations each appear of reasonable percentages to make determinations on the potential use of the product in the OTC marketplace.

⁸ 2011 U.S. Census QuickFacts Data (<http://quickfacts.census.gov/qfd/states/00000.html>); accessed August 17, 2012)

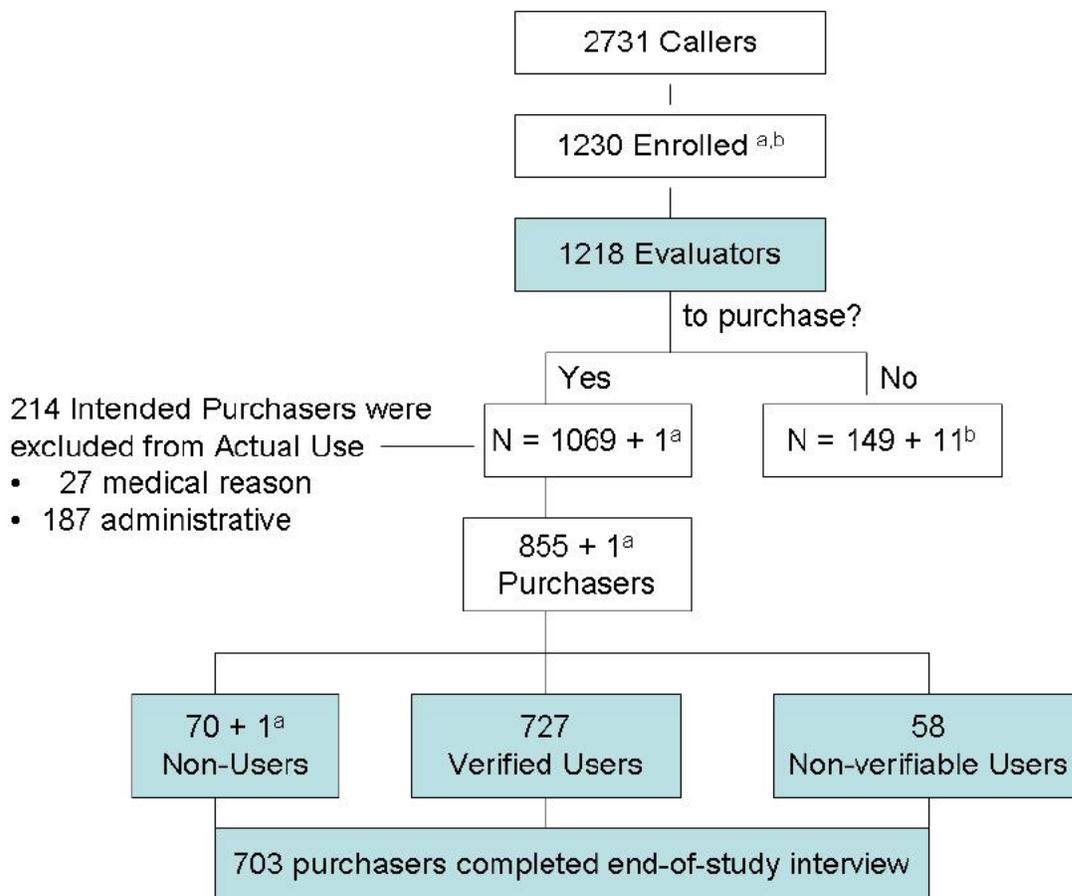
Table 7: Demographic Characteristics of Enrollment Population CL2008-13

	Evaluators (N = 1218)	Verified Users (N = 727)	Rejected from Purchasing (N = 214)	Non- Purchasers (N = 149)
Race and ethnicity				
White	886 (72.7%)	561 (77.2%)	131 (61.2%)	104 (69.8%)
Black or African American	140 (11.5%)	66 (9.1%)	34 (15.9%)	19 (12.8%)
Hispanic or Latino	132 (10.8%)	64 (8.8%)	41 (19.2%)	15 (10.1%)
Asian	18 (1.5%)	12 (1.7%)	1 (0.5%)	4 (2.7%)
Other	42 (3.4%)	24 (3.3%)	7 (3.3%)	7 (4.7%)
Education				
8th grade or less	17 (1.4%)	9 (1.2%)	4 (1.9%)	3 (2.0%)
Some high school	74 (6.1%)	35 (4.8%)	15 (7.0%)	14 (9.4%)
High school graduate, GED, or certificate	330 (27.1%)	178 (24.5%)	70 (32.7%)	41 (27.5%)
Some college or technical school	454 (37.3%)	283 (38.9%)	74 (34.6%)	48 (32.2%)
College graduate	250 (20.5%)	165 (22.7%)	36 (16.8%)	31 (20.8%)
Post-graduate degree	93 (7.6%)	57 (7.8%)	15 (7.0%)	12 (8.1%)
Age distribution				
Mean (SD)	57.9 (15.7)	58.4 (15.0)	56.1 (16.7)	61.2 (16.8)
Median	58	58	56	61
Range	18 - 94	18 - 94	18 - 92	18 - 92
Age groups				
18-20	13 (1.1%)	3 (0.4%)	2 (0.9%)	3 (2.0%)
21-30	57 (4.7%)	31 (4.3%)	14 (6.5%)	6 (4.0%)
31-40	93 (7.6%)	47 (6.5%)	21 (9.8%)	6 (4.0%)
41-50	217 (17.8%)	134 (18.4%)	42 (19.6%)	21 (14.1%)
51-60	303 (24.9%)	188 (25.9%)	48 (22.4%)	35 (23.5%)
61-70	250 (20.5%)	155 (21.3%)	46 (21.5%)	24 (16.1%)
71-80	190 (15.6%)	112 (15.4%)	20 (9.3%)	39 (26.2%)
81-90	92 (7.6%)	56 (7.7%)	20 (9.3%)	14 (9.4%)
> 90	3 (0.2%)	1 (0.1%)	1 (0.5%)	1 (0.7%)
Age 65 or younger	818 (67.2%)	494 (68.0%)	149 (69.6%)	81 (54.4%)
Age 65 or older	412 (33.8%)	238 (32.7%)	69 (32.2%)	69 (46.3%)
Age 75 or younger	1032 (84.7%)	618 (85.0%)	184 (86.0%)	114 (76.5%)
Age 75 or older	203 (16.7%)	121 (16.6%)	33 (15.4%)	36 (24.2%)
Normal literacy ^a	1042 (85.6%)	636 (87.5%)	173 (80.8%)	123 (82.6%)
Low literacy ^b	162 (13.3%)	89 (12.2%)	35 (16.4%)	20 (13.4%)
Missing	14 (1.1%)	2 (0.3%)	6 (2.8%)	6 (4.0%)
Abbreviations: GED = general education diploma, SD = standard deviation.				
^a Subjects scoring at least 61 on the REALM Test.				
^b Subjects scoring less than 61 on the REALM Test.				

Source: Applicant's submission, Module 5.3.5.1, Section 10.4, Table 8, p. 57

6.1.3 Subject Disposition

There were 2731 potential subjects who responded to the recruitment ads. See **Figure 4** and **Table 8** and **Table 9** for details on recruitment, enrollment, use and completion of the AUS.



a: One protocol violator

b: Eleven subjects with incomplete eligibility data

Source: Applicant's submission, Mod. 5.3.5.1, Section 9.7.1 Statistical Analysis Plan, p. 50.

Figure 4: Subject Disposition

Table 8: Screening Population - CL2008-13

Screening Population	N	% total
Began screening (callers)	2731	100%
Failed Inclusion/ Met Exclusion Criteria ¹	561	20.5%
Male	45	
Pregnant or may be pregnant?	5	
Employed by a pharmaceutical company?	9	

Clinical Review

Ryan Raffaelli, M.D.

NDA 202211

Oxytrol for Women® (Oxybutynin Transdermal System 3.9 mg/day)

Screening Population	N	% total
Employed by a pharmacy?	9	
Employed by an HMO or health insurance company as a healthcare professional?	50	
Employed by a healthcare practice?	81	
Ever trained or employed as a healthcare professional?	363	
Participated in market research studies, product label studies or clinical trials (1 yr)?	108	
All fields missing?	5	
Passed all screening questions?	2170	79.5%
Appeared at pharmacies to begin enrollment	1230	45% of total screened

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

Reviewer's comments: Questions 2-6 of the Screening Interview address exclusion criteria. If potential subjects answered "yes" to any of these questions, they were informed that they did not qualify for the study. Notably, no further questions were asked to inquire why male or pregnant subjects (n=50; 1.8% of screened subjects) wanted to use the product.

Table 9: Enrollment and Purchase Populations – CL2008-13

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

Enrollment and Purchase Populations	N	% total
Symptoms of UTI	3	
Other ³	6	(2.8%)
Purchase Decision = No	160	13.1%
Did not answer eligibility questions	9	
No medical exclusion	147	
Had medical exclusion to prevent use	4	(2.5%)
Narrow-angle glaucoma	0	
Hematuria	2	
Pregnant	0	
Breastfeeding	0	
Known oxybutynin allergy	1	
Symptoms of UTI	1	

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

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

³ These subjects did not sign the Informed Consent, refused the pregnancy test and did not have any additional data collected. Source: Adapted from Applicant's submission, Module 5.3.5.1, Section 10.1, Table 5, p. 53

As noted in **Table 8** and **Figure 4** above, 20% (N=214) of subjects who completed enrollment and wished to purchase the drug were excluded from entering the Use phase. Over 87% (n=187) of these patients were excluded for administrative reasons, i.e., refusing to sign consents, refusing pregnancy testing, ultimately deciding not to purchase the drug. Over 12% of the excluded subjects (n=27) had a medical reason for being excluded, and were referred to their physicians. These excluded subjects accounted for 2.5% of the total who wished to purchase the drug (27/1069). Most reported hematuria not related to menses, or other symptoms consistent with UTI (back pain and fever with hematuria, dysuria or cloudy urine). Of those, several completed a follow up interview, and many of them saw a healthcare professional based on the recommendation from trial personnel. Diagnoses included UTI (n=2), pre-diabetes, Type 2 diabetes, recurrent kidney stones, and irregular menstrual bleeding. The subject diagnosed with Type 2 diabetes is discussed in **Section 7.3.5 Submission Specific Primary Safety Concerns**. Others reported that hematuria was irregular, that they were already under a doctor's care, or that they understood the risks, but still wanted to try the product for their OAB symptoms. Subjects with narrow-angle glaucoma or who had a known allergy to oxybutynin stated that they chose to purchase the product hoping that it would successfully treat OAB symptoms, that they did not notice the label warnings, or that they misunderstood the label, i.e., believing that the usual anticholinergic side effects were signs of allergy to oxybutynin.

Of the 1069 who decided to purchase the drug, 230 subjects (21.5%) made that decision according to proposed labeling. Therefore, 839 subjects (78.5%) had

ineligibilities according to the label, but chose to purchase the drug, and, depending on the ineligibility, were allowed to do so. Label ineligibilities were contraindications or precautions proposed in the OTC label. The ineligibilities spanned the gamut, from not having two or more OAB symptoms for at least three months, to not having spoken with a doctor about symptoms or diagnoses such as weight loss, excessive thirst, liver or kidney disease. See below and **Section 7.3.5 Submission Specific Primary Safety Concerns** for comments on safety topics of interest as they relate to label eligibility and decisions to use the product.

Reviewer's comments: Because OAB is a diagnosis of exclusion, it is not adequate to allow OTC consumers to simply self-recognize OAB symptoms. Based on the high proportion (78.5%) of subjects who had label ineligibilities but chose to purchase and use the drug, it is clear that consumers' selection decisions are not ideal. FDA must be confident that consumers who make a decision to use the drug will not develop serious problems, since such problems might be averted in the Rx setting when consumers' physicians can oversee use of the drug.

Contraindicated symptoms or conditions include not having OAB or having a possible UTI (fever or chills with dysuria, or hematuria, or back or flank pain, or cloudy, foul-smelling urine), stress incontinence only, urinary or gastric retention, narrow-angle glaucoma, or allergy to oxybutynin. Subjects are cautioned to speak with their doctors if they have risk factors for diabetes (a history of diabetes in the immediate family, excessive thirst, extreme hunger, or increased tiredness), unexplained weight loss (conservative indicator of bladder cancer risk when reported with dysuria, hematuria and flank/back pain), history of kidney stones, or other liver or kidney disease.

Table 10 shows the purchase and use decisions of subjects reporting label ineligibilities. Of all subjects who completed enrollment procedures and evaluated the label (n= 1218), 931 (87.1%, 931/1069) who made a decision to purchase the drug met the condition of having two or more OAB symptoms for at least three months. As shown, the other 138 (12.9%) did not meet the OAB symptom conditions. Only 855 total subjects were dispensed the drug because 214 were excluded from the Use phase for medical or administrative reasons (see **Table 9**). Twelve percent (103/855) did not meet the OAB symptom conditions, but were allowed to use the drug because they met no exclusion criteria.

Table 10: Purchase and Use Decisions by Subjects with Label Ineligibilities^a

	Total Label Evaluators N=1218 (%) ^b	PD=Yes N=1069	Dispensed Drug N=855	Used Drug N=785 (%)	Spoke with Doctor & Used N=181 ^c
Label Ineligibilities - Indication					
<2 OAB symptoms or <3 months duration	179 (14.7)	138	103	88 (11.2)	11
Label Ineligibilities – Contraindications and Precautions					
Stress incontinence	315 (25.9)	281	214	198 (16.3)	Not reported
Possible UTI	260 (21.3)	229	166	154 (19.6)	19
Diabetes risk	516 (42.4)	454	351	321 (40.9)	79
Bladder cancer risk	188 (15.4)	163	107	100 (12.7)	12
Diuretic use	152 (12.5)	131	104	98 (12.5)	47
Liver/kidney disease	99 (8.1)	81	67	59 (7.5)	17
Incomplete emptying	522 (42.9)	458	357	323 (41.1)	3
Gastric retention, allergy, and/or narrow angle glaucoma ^d	36 (2.9)	35	21	20 (2.5)	0
Other OAB drug use	176 (14.4)	146	118	110 (14)	14

PD = Purchase Decision

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

b The total number of label evaluators following enrollment

c This was the total number of verified users who spoke to a doctor post-purchase around the time of initial use.

d Some evaluators reported more than one condition. No subjects reporting narrow angle glaucoma (n=4) or allergy (n=5) were dispensed drug, but only one of these subjects (allergy) said "No" to the purchase question.

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

Nearly 89% (697/785) of subjects who used the drug met the symptom conditions considered positive for OAB. Twenty-two of those who did not meet the conditions (12.3%; 22/179) reported having been told by their physician that they had OAB, and eight were already using an Rx OAB drug. Eleven used the drug. Most subjects appeared to understand the parameters of the proposed indication. Understanding the proposed symptom (> 2 symptoms) and duration (> 3 months) criteria of the indication may potentially limit delay in diagnosis of more serious medical conditions that can present with sporadic or single OAB symptoms, not necessarily indicative of idiopathic OAB.

There were 172 subjects (54.6%, 172/315) who reported having only stress incontinence, i.e., accidental urine loss when you cough, sneeze, or laugh, but otherwise met the labeled symptom conditions for OAB. Most of these subjects chose to purchase the drug (89.5%, 154/172) and many used it (72.7%, 112/154). Additionally, at least 60% of users with stress incontinence reported improvement of OAB symptoms at any of the weeks 3, 7 or 12 follow up interviews. Thirty-one (27.7%;

31/112) spoke with their doctors around the start of use, and, based on EOS interviews, over 60% were cleared to continue using the drug.

At the week 3 interviews, nearly 70% of the subjects who initially reported possible UTI-related symptoms indicated that their OAB symptoms had improved. The possibility of UTI, diabetes or bladder cancer mimicking OAB are further addressed in **Section 7.3.5 Submission Specific Primary Safety Concerns**.

The most frequently reported ineligibility was not being able to completely empty the bladder. Subjects were not specifically asked if they had “urinary retention.” The applicant believes that many consumers with OAB may feel that they cannot empty their bladders in efforts to explain their urinary urgency and frequency. Subsequently, the applicant revised the label to contraindicate use by consumers *who had been told by their doctor* that they had urinary retention. **Table 9** shows that only three subjects with incomplete emptying spoke with their doctors before use, thus supporting the assumed interpretation of subjects’ symptoms.

6.1.4 Analysis of Primary Endpoint

The primary endpoint was the proportion of subjects who did not stop Oxytrol® use when they developed either new or worsening symptoms. New symptoms were those indicated anywhere on the label plus abdominal or pelvic pain. The proportion was based on the total number of those who did not stop use from the population who used at least one patch (total user population). We determined another proportion defined as those with new or worsening symptoms who did not stop use from the total population reporting new or worsening symptoms.

Reviewer’s comments: We want to be sure that consumers will follow up with their medical providers to evaluate new symptoms or persisting/ worsening OAB symptoms. Idiopathic OAB is a diagnosis of exclusion and should be made in the absence of more serious medical pathology. Such follow up is part of current clinical practice. FDA expressed concern about delays in diagnosis of UTI, diabetes and early pregnancy, and potential risks associated with use of Oxytrol® if it is not indicated. Oxybutynin is not likely to improve symptoms often related to UTI or other diagnoses because mechanisms of pathophysiology differ.

The threshold rate for misuse by the primary endpoint was set at $\leq 5\%$. A study size of 531 subjects who use the test drug at least once provided 95% power to the trial to detect a 3.6% difference using a one-sided 97.5% confidence interval by the Exact Binomial Method. An interim analysis was conducted after the first 200 subjects completed the trial. The applicant employed mostly descriptive statistics to assess this endpoint.

The applicant employed mitigation strategies to determine whether subjects who reported new or worsening symptoms, but continued using the product, had a valid reason to do so (Question 2 of follow up and EOS interviews). An interviewer asked questions about symptoms at the week 3, 7 and 12 interviews. From diary entries, the applicant determined whether subjects who reported new or worsening symptoms continued use of the drug. Dates of use were recorded in the subjects' case report forms (CRFs). New symptoms were compared with symptoms listed in the label requiring subjects to stop use. Subjects who reported such a symptom were considered misusers by this endpoint.

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

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

These factors, and the applicant's mitigation strategy, are considered below in the analysis of the misuse rate threshold set to support safe and proper use of the drug. **Table 11** shows the number of subjects reporting any new symptoms, labeled, unlabeled, part of the mitigation process, or not. Additionally, the table indicates new symptoms, not otherwise specified or categorized, but coded by the applicant as "other." The table also shows the number of AEs reported by those subjects who reported "other" symptoms. We requested that the applicant submit a list of the subjects reporting new symptoms as "other" and their reported AEs. We wanted to determine whether any of the AEs included symptoms that would have qualified as indicating stopping use and, hence, misuse.

Table 11: Summary of Subjects who Reported Any New Symptom, Including "Other"^a, Not Otherwise Specified Symptoms, and Reported AEs.

	Week 3 Interview (N=741 completed)			Week 7 Interview (N=719 completed)			Week 12 Interview (N=693 completed)		
	New ^b	"Other"	AE	New	"Other"	AE	New	"Other"	AE
Number	240	155	155	227	134	134	213	151	150
Percentage (%)	NA	64.6	NA	NA	59	NA	NA	70.9	NA

NA = not applicable

^a The percentage of reported new symptoms coded as "other" is that of all new symptoms reported for that interview period.

^b The number of subjects reporting symptoms includes all labeled and unlabeled symptoms, listed as allowing mitigation and not. Source: Adapted from the applicant's submission; Module 5.3.5.1, Section 11.1.1.1, Tables 13, 14, 14-11-1 and 14-11-2, p. 68-69 and the applicant's AE questionnaire and AE datasets.

My review of the applicant's interpretation of user's interview responses revealed several subjects who reported pertinent AEs that may not have been captured by the applicant. These AEs may have indicated symptoms that should have triggered stopping use of Oxytrol for Women® as per the OTC label. For example, 12 subjects reported back or flank pain, but it is not clear whether these subjects were included in the misuse population. I evaluated results (proportion of misusers) based on mitigation assessments in the context of the clinical significance of potential risk to the consumer who reports new or worsening symptoms. We need to be confident that consumers who may have more serious medical conditions, not addressed by use of oxybutynin, will stop use and appropriately seek further medical evaluation.

Table 12 shows how the total number of users (verified and non-verifiable) responded after experiencing symptoms that should have indicated that they stop use. Report of new, labeled symptoms, abdominal or pelvic pain, or worsening symptoms should have resulted in stopping use and seeking a medical opinion. The table shows a comparison of the applicant's assessment, a proportion of the total users, and what's considered an exploratory proportion of a subgroup, one of users who had pertinent symptoms.

Table 12: Proportion of Subjects who did not Stop Use when they Developed New Symptoms or Worsening Symptoms - All Users

Primary Endpoint	Pre-mitigation (n=785) ¹	Post-mitigation (n=785)
Total users who had symptoms indicating stopping use	152 (19.4%)	152 (19.4%)
Total subjects who failed to stop use/ Total users of at least one patch (95% CI)	13.9% (109/785) (11.5%, 16.5%)	3.3% (26/785) (2.2%, 4.8%)
Total subjects who failed to stop use/ Total users who had symptoms indicating stopping use (95% CI)*	71.7% (109/152) (63.8%, 78.7%)	17.1% (26/152) (11.5%, 24%)

¹ All users included verified users (n=727) and non-verifiable users (n=58).

* This misuse rate was an exploratory, post-hoc, subgroup analysis.

Source: Adapted from Applicant's submission, Module 5.3.5.1, Section 11.1.1, Tables 13, 14 (p. 68, 69) and Table 14-14-1.

Reviewer's comments: Above, the applicant assessed misuse of all 785 users, of at least one patch, for the primary endpoint. The applicant calculated proportions of

misuse based on this denominator. The proportion of misuse of even a single patch was within the a priori threshold (3.3% < 5%), and the upper bound of the 95% confidence interval was also below the threshold. However, this does not appear to be clinically relevant. The applicant calculated a more relevant, albeit, exploratory proportion of a subgroup, i.e., those subjects who reported symptoms that should have led them to stop use and seek a medical opinion (n=152; 19.4%). The pre- and post-mitigation proportions of those who failed to stop use in this instance are much higher than the applicant's results. Data did not differ significantly from assessment of verified users only. Nearly 75% of these users reported misuse, pre-mitigation, whereas 17.7% (95% confidence interval: 11.8%, 25.1%) reported misuse, post-mitigation.

Nearly 20% of all users (n=152) reported symptoms or changes in symptoms that should have triggered them to stop use and seek a medical opinion. Further, of those who had symptoms, over 17% did not stop use when the label clearly directed them to do so. While the proportion of the subgroup may be more clinically relevant, the trial was not powered to determine significance of the misuse difference from the established threshold rate. The group of users reporting pertinent symptoms is not defined based on the baseline demographics, characteristics or medical conditions. Consequently, it is difficult to power a trial for this kind of subgroup analysis because it is unknown during the design stage of the protocol how many subjects will have developed the pertinent symptoms at the completion of the study. Therefore, the trial would have needed to be a great deal larger to capture enough patients with new or worsening symptoms, whereupon the alternative misuse rate might offer a more significant result.

This reviewer evaluated the applicant's rationale for mitigation of every subject who misused by the primary endpoint (n=91, total users included in datasets). For rationales that did not clearly meet one of the applicant's mitigation factors, I crosschecked the symptoms identifying misuse with AEs reported by the subjects. I agreed with the applicant's mitigations in all instances except two. Removing two subjects from the post-mitigation rate did not affect the final result. The misuse rate would rise to 3.6%.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints (SE) included

- SE1: proportion who did not stop use with new or worsening symptoms based on those who used the patch at least once. This proportion is similar to the primary endpoint, but does not include those who report abdominal or pelvic pain. The threshold rate for misuse was set at $\leq 5\%$ for this endpoint. Results did not differ from the primary endpoint since less than 20 subjects reported only abdominal or pelvic pain.
- SE2: median time to discontinue drug use by patients who do not experience improvement after two weeks of use. Duration of use, confirmed by diary, was at least 14 days between date of first patch use and interview date. This is not the same as 14 days of regular use as directed on the label.

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

Misuse by this endpoint was mitigated (EOS questions #10, 10a). Here, unlike for the primary endpoint, misuse was assessed by two employees of the applicant. If not in agreement, then a third reviewer (a physician employee) resolved the assessment. Subject responses mitigating continued usage beyond two weeks were pre-specified. One response pertinent to the applicant's refusal to include this as a primary endpoint was to mitigate if subjects indicated that symptoms were the same at the week 3 interview, but improved by the week 7 interview. The applicant mitigated use if subjects had considered that the drug may need a longer duration of use to exert an effect. The efficacy data supporting original approval showed that clinical effect may take 2-3 weeks, with most patients experiencing a benefit by three to six weeks possibly.

*Reviewer's comments: We need to be confident that consumers who have no improvement in symptoms after a reasonable duration of use, stop use and seek further medical advice. **Table 13** shows that the majority of subjects reported improved OAB symptoms at any follow up interview. However, of those who reported symptoms that stayed the same or worsened, the majority chose to continue using the drug. The most common reason (35.5%) was that subjects wanted to see whether an extended duration of use would result in a subjective clinical benefit. Subjects generally felt it was unnecessary to speak with their doctors to continue use beyond two weeks. Misuse was mitigated if subjects who reported no improvement, but who continued use beyond the week 3 interview, reported improvement at the week 7 interview. It does not appear that subjects who misused by this endpoint were at greater risk for AEs (see **Section 7 Review of Safety**).*

Table 13: Summary of Users' OAB Symptom Assessment and Action Taken

	Follow-up Week 3 (n=690)		Follow-up Week 7 (n=561)		Follow-up Week 12 (n=459)	
Number of Subjects who reported OAB assessment^a	690		559		458	
Improved	483	70%	354	63.3%	272	59.4%
Stayed the same ^b	187	27.1%	181	32.4%	171	37.3%
Continued use	137 (73.3%)		117 (64.6%)		146 (85.4%)	
Stopped use	50 (26.7%)		64 (35.4%)		25 (14.6%)	
Worsened ^b	20	2.9%	24	4.3%	15	3.3%
Continued use	12 (60%)		15 (63%)		11 (73%)	
Stopped use	8 (40%)		9 (37%)		4 (27%)	

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

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

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

Question 2 at the week 3 follow up interviews sought information from subjects who had OAB symptoms and had taken the drug at least once. Subjects were asked to compare the state of their symptoms, i.e., improved, the same or worse, from the beginning and the end of a two week period. Over 640 (n=643; 88.4% of verified users) subjects reported using the drug for at least two weeks. One hundred eighty seven (187; 29.1%) verified and non-verifiable users reported a lack of improvement in symptoms (both no change and worsening symptoms). Of these, 145 (77.5%) failed to stop use as directed. Post-mitigation, 71 (38%) had continued use after two weeks without improvement. The applicant indicates that many of these subjects were willing to continue use to see if it began to work.

Reviewer's comments: The applicant determined proportions of subjects without improvement who did not stop use, based on the total number of subjects who took the drug for two weeks. This resulted in percentages of 22.6% and 11%, pre- and post-mitigation, respectively. A post-hoc, exploratory proportion of a subgroup considers subjects who had no improvement but continued use derived from the total number of subjects who took the drug for two weeks with no improvement (no change or worsening). Here, the results are 77.5% and 38%, pre- and post-mitigation, respectively.

Because idiopathic OAB is a diagnosis of exclusion, it is important for consumers with persistent symptoms to seek appropriate medical evaluation. Results here show that many subjects continue to use the product even when the label clearly instructs stopping use and seeing a physician beyond two weeks without an effect.

The applicant also conducted an analysis combining misuse rates by the primary endpoint and SE3. Overall, 219 subjects (30.1%; 219/785) did not stop use with new or worsening symptoms or after two weeks without improvement. The post-hoc proportion of a subgroup, 79.3% (219/276), was those users who failed to stop use derived from those who had pertinent symptoms as per either endpoint. Post-mitigation, the proportion declined to 89 (12.2%; 89/785), but was 32.2% (89/276) by the proportion of the subgroup. Reasons why caution must be exercised when interpreting these results are similar as those for the primary endpoint.

- SE4: proportion of case outcomes in specific categories. Subjects with new, worsening or unchanged symptoms who continued on therapy had their symptom risk categorized as “medical risk,” “possible medical risk,” or “minimal/insignificant risk.”

Reviewer’s comments: FDA informed the applicant (letter; November 15, 2010) that we did not agree with the stratification categories and would not consider them in our evaluation.

- SE5: proportion of subjects who misused based on incorrect duration (> 4 days) and/or incorrect simultaneous, multiple patch use (> 1 patch per application). Misuse was mitigated. Subjects with diaries that were missing starting or ending dates were excluded. If misuse showed any type of pattern, it was not mitigated.
 - At the EOS interview, subjects were asked how many days they were allowed to wear a single patch (Questions #14, 14a, 14b) and how many patches they were allowed to wear at the same time (Questions #13, 13a). The mitigation review process was similar to that for SE3. Subjects who used patches for longer than 4 days had to meet all of the following criteria to be mitigated:
 - No patch was used for ≥ 8 days
 - Two or fewer patches were used for 6-7 days
 - Total number of patches misused $\leq 25\%$ of total patches used
 - Subject gave a valid reason for misuse, e.g., “I forgot to remove.”

Reviewer’s comments: Consumers who wear a patch for longer than directed may be at risk for worse application site reactions. However, such reactions are usually self-limited and consumers may simply remove the patch if their skin becomes irritated. Use of multiple, simultaneous patches may have greater risk for adverse drug reactions, including anticholinergic-related events, particularly CNS-related events, and overdose. Such use could be particularly dangerous for elderly consumers who are more likely to use the drug.

Pre-mitigation, 370 (50.9%, 370/727) misused at least one patch based on prolonged duration and/or simultaneous use. See **Table 14** for misuse rates for SE5. Of note, 34 subjects (4.7%) misused by a combination of prolonged and simultaneous use. There are six subjects missing from the total users who misused by separate methods

(333+77= 410 – 370= 40 – 34= 6). Twenty seven subjects who misused by simultaneous use only (27/77; 35.1%) were over age 65. Misuse was mitigated for all of them but seven. Additionally, the applicant notes that individual patches were applied correctly, as per diary entries, 84.9% and 95.9% of the time for prolonged duration and simultaneous use misuse, respectively. The vast majority of subjects had few and often sporadic misuses of patches over their total duration and quantity of use.

Table 14: Proportion of Subjects who Misused the Patch as per SE5

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

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

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

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

Of subjects who misused by both methods, only simultaneous use by six was not mitigated. Frequently reported reasons for prolonged use included “forgot to remove the patch” (n=165; 50% of those who provided a reason at the End-of-study interview, 165/330), denial of prolonged use (n=93; 28.2%), and misunderstood label directions (n=38; 11.5%). For simultaneous use, most subjects denied misuse (n=59; 85.5% of those reporting reasons, 59/69), or reported only replacing a patch (n=7; 10.1%). Three reported forgetting to remove the prior patch. As per the pre-specified mitigation reasons, forgetting to remove the patch, denying misuse, i.e., discrepancies in diary entries, and same-day patch replacement were allowed for mitigation.

Reviewer's comments: Other reasons for misuse by either method are not mitigated (n=82/330 who reported any reason; 24.8%), including misunderstanding the label (n=39; 9.8%), inconvenience (n=19; 5.8%), to help with symptoms (n=3; 4.3%), and other, unidentified reasons (n=21; 5.3%). Most unmitigated misuse was for prolonged use, and subjects may have reported more than one reason for misuse. These reported reasons may indicate a lack of understanding of the proposed label directions, and of the severity of warnings and precautions on the label.

I reviewed a line listing table of all users that misused the product based on SE5. The table was not provided in the original NDA, but was requested by FDA upon filing the application. On September 6, 2012, the applicant submitted an amended table with further comments on individual reasons for misuse and mitigation. Misuse by a few subjects was recoded to “mitigated” or “unmitigated” based on further review of

responses to End-of-Study questions. The changes did not greatly affect the overall results.

I specifically reviewed the reported reasons for misuse by simultaneous use from a total of 89 listed subjects. It is not clear why the applicant identified only 77 total misusers by this method. My review did not result in changes to the applicant's post-mitigation misuse rates. As stated in the description of the mitigation strategy, the applicant mostly utilized the diary entries to define simultaneous use. Of note, at the EOS interview, many subjects were not asked about their questionable or discrepant diary entries to confirm recording errors. Only 69 (77.5% of misusers by this method) verified users were asked the EOS question (#13) "How many patches did you understand you could wear at a time?" All 69 responded, "one." A large majority responded to a follow up question (#13a) about simultaneous use with a denial of such use, or a comment that they were replacing an old patch or had forgotten to remove an old patch. Four responded that they used multiple patches simultaneously because they thought it would help with symptoms, or misunderstood the label. The large majority understood that a single patch should be applied for four days (86.2%).

From my review, the total unmitigated misuse rate by the potentially more serious simultaneous use was only 4.5% (4/89). It appears unlikely that consumers will use multiple patches simultaneously to achieve relief of their OAB symptoms in the OTC setting. Based on my review, it does not appear that consumers will regularly misuse by prolonged duration or simultaneous use.

6.1.6 Other Endpoints

Adverse events will be discussed in **Section 7 Review of Safety**. AEs reported by users were analyzed separately from subjects who were excluded following a purchase decision and subjects who purchased but never used the product.

6.1.7 Subpopulations

The applicant assessed the primary endpoint, SE3 and SE5 by literacy (normal versus low (<60 on REALM)), age (<65 years, 65-74 years, ≥ 65 , and ≥ 75 years), and race (whites versus non-whites). The applicant reports that there were no notable differences observed in the subgroups. Some subgroups had low sample sizes and, therefore, results may not be generalizable to the population of likely users.

Table 15 compares the rates of misuse by race, age and literacy for the primary endpoint. The shaded rows show the applicant's per protocol endpoint (among all verified users, the % who fit the race, age or literacy criteria, and who had new or worse symptoms and did not stop use). The unshaded rows show the post-hoc proportions of subgroups who fit the race, age or literacy criteria and reported pertinent symptoms.

Table 15: Proportion of Subjects who Misused by Race, Age or Literacy for the Primary Endpoint¹

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

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

* These misuse rates are exploratory, post-hoc, subgroup analyses.

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

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

Reviewer's comments: Above, the applicant assessed misuse of all 727 verified users for the primary endpoint. Although some of the subgroups have small sizes, nearly 20% of all verified users reported symptoms or changes in symptoms that should have triggered them to stop use and seek a medical opinion. Post-mitigation, of those who had symptoms that should have indicated stopping use (unshaded rows), at best, 6.7% (low literate) and at worst, nearly 28% (non-white), did not stop use when the label clearly directed them to do so.

Table 16 compares the rates of misuse by race, age and literacy for SE3. The shaded rows show the applicant's per protocol endpoint (among all verified users, the % who fit the race, age or literacy criteria, and who had no improvement of OAB symptoms, used the drug for two weeks, and did not stop use). The unshaded rows show the post-hoc proportions of subgroups who fit the race, age or literacy criteria, used the drug for two weeks, and reported no improvement of OAB symptoms.

Table 16: Proportion of Subjects who Misused by Race, Age and Literacy for SE3¹

SE3 (N=643)	Total Misusers – pre-mitigation		Total Misusers – post-mitigation	
Race	N	% total w/ no improvement	N	% total w/ no improvement
White* (n=151)	122	80.8% (122/151)	60	39.7% (60/151)
(Applicant) proportion - White (n=496)		24.6% (122/496)		12.1% (60/496)
Non-white* (n=36)	23	63.8% (23/36)	11	30.5% (11/36)
(Applicant) proportion - Non-white (n=147)		15.6% (23/147)		7.5% (11/147)
Age	N		N	
< 65 years* (n=113)	85	75.2% (85/113)	42	37.2% (42/113)
(Applicant) proportion < 65 years (n=431)		19.7% (85/431)		9.7% (42/431)
65-74 years* (n=38)	31	81.6% (31/38)	13	34.2% (13/38)
(Applicant) proportion - 65-74 years (n=104)		29.8% (31/104)		12.5% (13/104)

SE3 (N=643)	Total Misusers – pre-mitigation		Total Misusers – post-mitigation	
≥ 65 years* (n=74)	60	81.1% (60/74)	29	39.2% (29/74)
(Applicant) proportion ≥ 65 years (n=212)	28.3% (60/212)		13.7% (29/212)	
≥ 75 years* (n=36)	29	80.5% (29/36)	16	44.4% (16/36)
(Applicant) proportion ≥ 75 years (n=108)	26.9% (29/108)		1.8% (16/108)	
Literacy²	N		N	
Literate* (n=167)	129	77.2% (129/167)	65	38.9% (65/167)
(Applicant) proportion Literate (n=571)	22.6% (129/571)		11.4% (65/571)	
Low literate* (n=20)	16	80% (16/20)	6	30% (6/20)
(Applicant) proportion Low literate (n=70)	22.9% (16/70)		8.6% (6/70)	

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

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

* These misuse rates are exploratory, post-hoc, subgroup analyses.

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

Reviewer's comments: The applicant determined proportions of misuse for SE3 by age, race and literacy subgroups. As above, the post-hoc proportion (FDA's proportion) of the subgroup is based on those subjects who used the drug for two weeks, and reported no improvement, i.e., no change or worsening (n=187; 29%). The proportions of those who failed to stop use in this instance are much higher than the applicant's rates.

The Table above shows that subjects misused at a high rate, never below 30% for any subgroup even after mitigation of reported misuse. From review of the applicant's line listing of misuse by SE3 (Table 14-14-45 in submission; n=144), it also appears that many subjects were mitigated based on responses at the week 7 interviews. Subjects who reported no improvement at week 3, following two weeks of use, but had improvement at week 7 were mitigated if they offered a "thoughtful, informed reason," as per the pre-specified mitigation criteria, to continue use. The proportions may indicate that many subjects continued use beyond two weeks to see whether the product needed more time to become effective. Alternatively, it may indicate that subjects do not heed the warnings to seek medical evaluation for more serious diagnoses such as diabetes, bladder cancer, etc. However, the safety data does not

show that these users were at any greater risk of AEs or delays in diagnosis of other conditions if they used the drug beyond two weeks without seeking medical advice.

The applicant also assessed the median time to discontinue use by users reporting no improvement after two weeks' use. Subjects who reported worsening symptoms at week 3, the median number of days to discontinue was 8.5. For subjects reporting no change at week 3, the median was 36 days. Many subjects who had no change in symptoms at week 3 chose to continue using the product even if the label clearly instructed them to stop use and see a physician. If misuse was unmitigated for these subjects, that meant that they had not spoken with a doctor before choosing to continue use beyond two weeks.

Table 17 compares the rates of misuse by race, age and literacy for SE5, the proportion of subjects who misused based on incorrect duration (> 4 days) and/or incorrect simultaneous, multiple patch use (> 1 patch per application). Rates of misuse increase with age (18.3% to 28.6% post-mitigation). The table also shows rates by simultaneous use alone (sim. use only). There were low numbers of subjects misusing by only this method.

Table 17: Proportion of Subjects who Misused by Race, Age and Literacy for SE5

SE5 (N=727)	Total Misusers – pre-mitigation			Total Misusers – post-mitigation		
	Race ¹	N	% total (95% CI)	Sim. Use only (%)	N	% total (95% CI)
White (n=553)	301	54.4% (50.2%, 58.6%)	60 (10.8%)	129	23.3% (19.9%, 27.1%)	17 (3.1%)
Non-white (n=163)	69	42.3% (34.6%, 50.3%)	17 (10.4%)	23	14.1% (9.2%, 20.4%)	5 (3.1%)
Age²						
< 65 years (n=481)	226	47% (42.5%, 51.6%)	50 (10.4%)	88	18.3% (14.9%, 22%)	15 (3.1%)
65-74 years (n=116)	68	58.6% (49.1%, 67.7%)	15 (12.9%)	30	25.9% (18.2%, 34.8%)	5 (4.3%)
≥ 65 years (n=235)	144	61.3% (54.7%, 67.5%)	27 (11.5%)	64	27.2% (21.6%, 33.4%)	7 (3%)
≥ 75 years (n=119)	76	63.9% (54.6%, 72.5%)	12 (10.1%)	34	28.6% (20.7%, 37.6%)	2 (1.7%)
Literacy³						
Literate (n=629)	325	51.7% (47.7%, 55.6%)	65 (10.3%)	133	21.1% (18%, 24.5%)	18 (2.9%)
Low literate (n=86)	44	51.2% (40.1%, 62.1%)	12 (14%)	18	20.9% (12.9%, 31%)	4 (4.7%)

¹ The total number under "Race" = 726. One subject may not have indicated race.

² The total number under "Age" = 716. Eleven subjects may not have reported age.

³ The total number under "Literacy" = 716. Eleven subjects may not have completed the REALM test.

Reviewer's comments: Overall, the subgroup proportions did not appear to differ greatly. While rates for subjects 65-74 and low literate subjects were highest, these categories included the lowest total numbers of misusing subjects.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Dr. Gierhart's and Dr. Batra's reviews of the original NDA.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See Dr. Gierhart's and Dr. Batra's reviews of the original NDA. Also see pertinent discussion in **Section 6.1.5 Analysis of Secondary Endpoints(s)** under the subsection for secondary endpoint 3. There, I weighed the typical onset of clinically meaningful effect against the labeled safety instruction to stop use and see a doctor if OAB symptoms do not improve after two weeks' use.

7 Review of Safety

Safety Summary

Safety assessment for proposed switches of Rx drugs to OTC marketing status requires evaluation at several levels. Ultimately, recommendations for approval hinge on whether the results of the overall analysis can be adequately communicated in Drug Facts labeling. For Oxytrol for Women®, this reviewer evaluated the following:

- The target population (women over age 18) and adequacy of the proposed indication
- Women without contraindications selecting to use the drug
- Women who have symptoms or medical history needing the advice of a doctor to determine whether the drug is appropriate to use
- Compliance with labeled criteria to stop use
- Safety topics of interest, i.e., possible symptoms of UTI, diabetes risk factors, bladder cancer risk factors, early pregnancy, urinary or gastric retention, allergy, glaucoma, skin reactions, anticholinergic effects, disorientation or confusion, and falls or accidents
- Postmarketing experience

The drug should not be targeted for use by men since prostate disease is not self-identifiable. A very small number of men inquired about using the drug. Nearly 80% of women who wished to purchase the drug had at least one symptom, condition or medical history concern that should have caused them to not use the drug or to seek the advice of a doctor (**Table 10**). Most of these ineligibilities were minor. Most frequently, over 42% of those with ineligibilities reported either incomplete bladder emptying (urinary retention) or diabetes risk factors. For the former, the label was revised to address likely misunderstanding of how urinary retention is defined and diagnosed. The latter are nearly ubiquitous in the U.S. Nearly 23% of users reported possible symptoms of UTI; however, only 12 of these subjects were diagnosed with UTI, and all but one recognized their symptoms early and sought medical attention. A small percentage of subjects reported bladder cancer risk factors, but the warnings are very conservative and non-specific. See **Section 7.3.5 Submission Specific Primary Safety Concerns** for further details on safety topics of interest.

This reviewer evaluated the adequacy of the proposed indication, selection to use if subjects reported contraindications or precautions to use, and compliance with labeled warnings to stop use, all in the context of the safety data from the CONTROL trial (**Section 7.3 Major Safety Results**) and postmarketing (**Section 8 Postmarket Experience**). Nearly 66% of all users reported an AE (n=519), and 35 reported 48 SAEs. The most commonly reported AEs were application site reactions and anticholinergic effects (dry mouth and constipation). Users < 65 years of age reported application site reactions and constipation most frequently, while those > 65 years of age frequently reported UTI and dysuria. Over 27% of those who reported AEs

discontinued the drug because of them, and the most commonly reported AE by these users was application site reactions. Similarly, postmarketing experience indicates that application site reactions and anticholinergic effects are most commonly reported, particularly dry mouth, blurry vision, dizziness and constipation. The safety databases and published literature do not indicate that there are significant delays in diagnosis of other serious conditions with use of oxybutynin. Similarly, there were no patterns of poor selection or misuse that resulted in particular adverse events.

Regarding the risk of delaying diagnosis of more serious conditions, I more heavily considered whether consumers are likely to confuse idiopathic OAB with UTI. It does not appear so. There were 66 UTIs or bladder infections diagnosed during the trial. Five were included in serious reports. Almost all of these users recognized their symptoms early, or did not report any symptoms that would be more typical of UTI (dysuria, fever, flank or pelvic pain). Most also reported long term OAB symptoms (including all those with SAEs), upwards of several months, effectively eliminating the likelihood that those users were suffering from acute UTIs at the time of purchase. The applicant's electronic health records' review shows that it is uncommon for people, without typical symptoms of UTI, to be diagnosed presenting only with OAB symptoms. Short duration of OAB symptoms could, however, indicate a diagnosis such as UTI, but less than 3% of all those who evaluated the label reported OAB symptoms of less than one month, and fewer chose to purchase and use the drug.

Diabetes, another serious condition that may present with OAB symptoms, is more frequently asymptomatic. Use of Oxytrol for Women® appears unlikely to significantly delay diagnosis of diabetes. Description of the two new diagnoses of diabetes in the CONTROL trial (**Section 7.3.5**) supports this notion. Bladder cancer, another mimicking condition, more commonly occurs in males and frequently presents with painless, gross hematuria. Comparison of urinary symptoms with OAB is distinctive (**Table 23**), and no cases were reported in the trial. Finally, women with early pregnancy may have OAB symptoms, but the proposed label definition indicating three month's duration of symptoms, and labeled warnings not to use if pregnant should limit use by this population. Also see **Sections 7.6.2 Human Reproduction and Pregnancy Data** and **8 Postmarket Experience** for details on safety in pregnancy. My focus on other safety topics of interest did not identify any new safety signals, although, the risk for CNS-related anticholinergic effects, and the potential for resultant falls or accidents, is important to consider, and is addressed in **Section 9.2**

Labeling Recommendations.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The CONTROL trial assessed use and safety of Oxytrol for Women® in a naturalistic OTC environment. All subjects who said “yes” to purchase and who completed at least one follow up interview were included in the primary safety analysis. A separate safety analysis was conducted for excluded subjects who said “yes” to purchase. These subjects were also followed to determine whether they received any medical diagnoses based on their reasons for exclusion.

7.1.2 Categorization of Adverse Events

Verbatim descriptions were provided in the applicant’s datasets. The applicant established adverse event categories (source: MedDRA Version 11.1), or sub-populations, reflecting several primary safety concerns and linked to the verbatim descriptions. Terms appeared reasonably thorough.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Clinical trials conducted to support approval of the original NDA included a phase 2 dose-ranging trial, and two phase 3 trials. In those studies, over 660 subjects with OAB symptoms, and 83 healthy volunteers were exposed to at least one application of transdermal oxybutynin. Duration of exposure in controlled trials and open-label extension periods averaged 150.5 days (range 1-428). The mean age of subjects was 62 years (18-89) with 46% over age 65. Most (91%) patients were female and Caucasian. As noted elsewhere, based on sales information, there has been nearly 275,000 patient years of exposure to Oxytrol® since its approval in 2003. In the recently conducted AUS, 785 subjects (727 verified users; 58 non-verifiable users) applied at least one dose of the proposed drug. Based on diary data, median exposure was 45 days (mean = 45 ± 27.3 days (SD)).

The Office of Surveillance and Epidemiology evaluated drug utilization in the prescription setting (DARRTS; October 15, 2012). Its review indicated that from 2003-

2011, about 2.2 million total prescriptions of Oxytrol® were dispensed to over 480,000 patients. From available data, most users are female (82.5%) with mean and median durations of use of two and one month, respectively. Patients > 65 years of age received 62% of all prescriptions over the review period. About 75% of patients filled prescriptions for a total use duration of ≤ two months. Only 1% had treatment episodes lasting beyond one year.

Reviewer's comments: Drug exposure has been adequate to support safe use. Interestingly, Oxytrol® does not appear to be used chronically by most patients in the Rx setting.

7.2.2 Explorations for Dose Response

Not applicable. See Dr. Gierhart's and Dr. Batra's reviews of the original NDA.

7.2.4 Routine Clinical Testing

Serum pregnancy testing (human chorionic gonadotropin; HCG) and EOS urinalysis were the only clinical testing performed. Results from these tests are evaluated elsewhere.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events reported in completed clinical trials for original approval of this NDA, and in several postmarketing databases, identify AEs related to use of anticholinergic drugs. These include constipation, dry mouth, nausea, urinary hesitancy and retention, blurry vision, drowsiness, palpitations, dizziness and impotence. Oxytrol for Women® was proposed for OTC use for treatment of OAB symptoms because the transdermal formulation is believed to have a lower rate of risk for such symptoms due to bypass of first pass metabolism and limited production of the active metabolite, NDEO. Although, because the product is applied to the skin, the most common AEs are skin-related with erythema, irritation and pruritis most frequently reported.

7.3 Major Safety Results

7.3.1 Deaths

There was one death. The subject (ID# 24-0092) had a history of HIV infection and died of complications from acute viral pneumonia. It is unclear if she had been using the patch at the time of her death.

7.3.2 Nonfatal Serious Adverse Events

Forty one subjects reported 48 SAEs over the duration of the trial. Only one was considered possibly related to the study drug by the applicant's assessment. This subject (ID# 35-0037) had surgery on a rotator cuff. She did not completely recover from anesthesia in the post-operative period (Preferred Term – anaesthetic complication), and she had been wearing a patch at the time. A drug interaction was considered possible. Thirty five subjects with SAEs were users, five were nonusers and one subject purchased the product but was not dispensed the drug. This subject had hematuria and was excluded from the Use phase, but her SAE was back pain due to kidney stones. The applicant states that SAEs included three UTIs, three strokes, four cases of back or chest pain, and two diagnoses of cholecystitis as the only reports made two or more times. This reviewer checked the narratives and found two additional subjects reporting UTIs (see **Section 7.3.5 Submission Specific Primary Safety Concerns**).

*Reviewer's comment: This reviewer analyzed the SAE narratives. While no events seemed related to use, I believe that a few more events may be considered possibly related to use of the drug. Subject 12-0039 reported transient arrhythmia with tachycardic episodes noted during a sleep study while using the drug. She had a history of hypertension and hypercholesterolemia. Two users reported stroke during the use phase (ID# 14-0009 and 37-0153). One subject reported hypertension and history of prior stroke, but there were insufficient additional details to determine the potential causes of the strokes. It is possible that arrhythmias could be implicated. Another subject (ID# 24-0037) reported a syncopal episode due to hypotension which could have been instigated by tachycardia due to oxybutynin use. Whether warnings for consumers with cardiac disease should be included in labeling is a matter for further discussion. See **Section 9.2 Labeling Recommendations**. It does not appear that any of the reported SAEs identify safety signals which would preclude approval of Oxytrol for Women®. See **Section 7.3.5** for more details on all SAEs included in the safety topics of interest.*

7.3.3 Dropouts and/or Discontinuations

Subject participation in the AUS could be terminated if

- the subject had a significant protocol violation.
- the subject reported an SAE.
- the subject requested to discontinue participation.
- the subject reported blood in the urine unrelated to menses, and/or had back pain and fever with OAB symptoms and dysuria, hematuria or cloudy urine.
- the investigator deemed it necessary to protect the subject or to deal with "unmanageable" factors that may interfere with the trial or interpretation of results.

Of the entire safety population (n=785), 152 (19.4%) permanently discontinued the test drug; 141 (18%) discontinued due to any AE, 17 due to SAEs. This was 27.2% of all those who reported at least one AE (141/519). Thirty one subjects (28.2%), reporting an AE at least possibly related to use of the test drug, were > 65 years of age. The differences, by age, between subjects who permanently discontinued use of the study drug for any reason or due to AEs were not significant. Most of the 141 who discontinued use of the test drug participated in follow up interviews for the duration of the full trial. Only six subjects (0.8%) permanently discontinued participation in the trial due to an AE (application site reactions (n=2), allergic reaction, sleepiness, constipation and lightheadedness). None of these AEs were serious. The applicant also reports that 60 subjects were lost to follow up and 49 withdrew consent.

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

*Reviewer’s comments: The proportion of discontinuations and AEs identified as the causes for discontinuing use of the drug or from any participation in the remainder of the trial do not raise concern for new safety signals. See **Section 7.3.5 Submission Specific Primary Safety Concerns**.*

7.3.5 Submission Specific Primary Safety Concerns

Possible symptoms of Urinary Tract Infection (UTI)

Over 20% of label evaluators reported at least one label ineligibility that could be consistent with UTI:

- pain or burning when urinating
- fever or chills in conjunction with pain or burning when urinating
- hematuria
- cloudy or foul-smelling urine
- lower back or side pain

Most of these subjects (**Table 18**) were still allowed to enter the Use phase, as only three met the exclusion criteria of back pain with or without fever and either dysuria, hematuria or cloudy urine. Thirteen others were excluded from the Use phase for reporting isolated hematuria unrelated to menses.

Table 18: Actions of Subjects with Possible UTI Symptoms Following Purchase Decision – Enrollment Interview

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

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

^b Total users

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

Of the subjects who reported possible UTI symptoms at the enrollment interview, and used the patch (n=154), only eight were diagnosed with a UTI (5.2%) over the course of the trial. Seven of these subjects recognized the symptoms or were diagnosed through routine care, i.e., by urinalysis at an office visit. The last subject was diagnosed based on the EOS urinalysis. Only one of these subjects’ UTIs was categorized as an SAE (ID# 31-0006). This subject had reported foul-smelling urine at enrollment. During the Use phase, she was diagnosed with and hospitalized for treatment of UTI and sinusitis. She also reported mental status changes (hallucinations and confusion) that persisted beyond resolution of her illnesses. An additional 26 subjects reported symptoms of possible UTI over the course of the trial. Nearly 58% stopped using the patch, as directed. The remainder of them continued using the patch, but most of this misuse was mitigated. Four of these users with new symptoms were diagnosed with UTI, none were SAEs.

This reviewer also considered the duration of reported OAB symptoms to help distinguish between UTI and idiopathic OAB. Subjects with shorter duration of symptoms may be more likely to have acute UTI versus OAB. The large majority of all enrollees reported having OAB symptoms for at least three months, making it unlikely that symptoms were due to an emerging UTI. While 179 subjects (14.7%) with either a short duration or less than two OAB symptoms reviewed the label, most who ultimately made a decision to purchase were those who had < 2 OAB symptoms, but for three or more months. In addition, based on review of the enrollment interviews, very few subjects (n=33) reported symptoms for equal to or less than one month, further limiting the likelihood that symptoms were UTI-related. Five subjects who did not meet the OAB symptom conditions were diagnosed with UTI or bladder infection over the course of the trial; however, four diagnoses came at least three weeks after first patch application. The fifth subject (ID#11-0085) reported burning on urination on her first day of patch application. She had reported having OAB symptoms for two months, and did not report symptoms consistent with UTI during enrollment. Five days after initial use, she presented to her physician and was diagnosed with a UTI and yeast infection and treated. She discontinued use of the drug, and did not continue the trial. All five of

these users recognized their symptoms and spoke with their healthcare providers when the symptoms began. Only two continued using the drug.

In total, 61 subjects (7.8%) reported UTIs or bladder infections (n=66), sometimes multiple infections, over the duration of the trial. Five of these infections affected subjects reporting SAEs. Two UTIs were considered serious themselves; the others were identified in serious reports. The two serious UTIs were managed by hospitalization and intravenous antibiotics; neither was reported with sepsis, nor were upper urinary tract complications indicated. From review of the narratives and CRFs, the others appeared to be incidentally diagnosed in subjects undergoing in-hospital management of other events (pelvic inflammatory disease, recurrent bloody diarrhea and surgery for pelvic prolapse). Two stopped use of the drug at the time of their diagnosis. Another had discontinued use a few days prior to diagnosis due to skin irritation. Two continued use after treatment. The OAB symptoms, for all five subjects, ranged in duration from 8 months to 20 years. Only one subject had any UTI-like symptoms (foul-smelling urine) upon enrollment.

Finally, 461 subjects (453 total users (58%) and eight non-users) returned for the EOS urinalysis at their pharmacy sites. Nearly 49% (n=225) had at least one positive result (blood, protein, glucose, nitrite, or leukocytes). Two hundred twenty (220) completed the Use phase follow up interviews for these urinalyses. An additional 69 subjects completed this interview as well; 68 reported seeing their MD for a labeled precaution or condition, and one had been withdrawn from the study due to her report of possible UTI symptoms indicating exclusion from the Use phase. Of those who had a positive urinalysis, 146 (50.5%; 146/289) reported seeing their healthcare provider after receiving the results. The applicant reported that 20 verified users were subsequently diagnosed with UTI or bladder infection based on results of the EOS urinalysis. I reviewed the medical summaries of all 146 subjects who followed up with their physicians. More than 55 UTIs or bladder infections were diagnosed or treated. Many subjects appeared not to report any symptoms, as several of the diagnoses were made on the results of the urinalysis alone. However, a few other subjects who reported symptoms and had positive urinalyses did not report receiving any treatment.

Reviewer's comments: While some subjects who chose to purchase and use the drug had at least one symptom that could indicate a UTI, the majority of subjects reported having OAB symptoms for more than one month. Symptoms of acute UTI would not likely be tolerated by most persons for that length of time. It appears that the few subjects who had shorter term OAB symptoms and UTI recognized the symptoms and sought medical evaluation. Additionally, the fact that so few users, reporting symptoms of possible UTI at enrollment, spoke with their doctors prior to use (19/154, 12.3%) may further support consumers' ability to distinguish symptoms of UTI from OAB. Of the 61 subjects with UTI or bladder infection, only eight reported possible UTI symptoms at the enrollment interview, and seven of these recognized the symptoms. The one subject diagnosed only at EOS had used the drug for three weeks prior to diagnosis and had

reported OAB symptoms, at enrollment, that had been ongoing for 10 years. Many subjects diagnosed with UTI appeared not to have typical symptoms at enrollment or throughout the use phase of the trial. The EOS urinalysis results and narratives show how variable diagnosis of UTI may be.

UTIs are fairly common in the older female population who are most likely to use this product⁹. We must be confident that consumers can recognize symptoms of UTI, distinguish them from OAB, and seek medical attention. 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.

Incomplete Bladder Emptying (Urinary Retention)

A large majority of subjects who chose to purchase the drug had label ineligibilities of lesser significance than absolute contraindications. The most frequently reported ineligibility was the feeling of not being able to completely empty the bladder. Subjects were not specifically asked whether they had “urinary retention” because the applicant felt that this was not consumer-friendly language. Of 522 users (66.5%; 522/785) who reported this feeling, only three spoke with their doctors prior to use. The applicant believes that OAB sufferers may explain their increased urinary frequency and urgency as indicative of an inability to empty their bladders, or the perception that they are retaining urine. Based on these results, the proposed OTC label was revised to more specifically warn consumers not to use the drug if they have ever been told by a doctor they have urinary retention (an inability to empty one’s bladder), therefore limiting possible misunderstanding.

Six subjects reported instances of new or worsening “urinary retention” over the duration of the trial. One of these subjects (ID# 37-0142) had a history of incomplete bladder emptying prior to use. This subject reported speaking with her doctor about the symptoms before continuing use of the drug. Another subject (ID# 24-0006) reported “retention” within a few days of use. She discontinued use of the drug on the advice of her doctor. None of the reports indicated that any urologic diagnoses of acute urinary retention were made. All were more consistent with similar misunderstanding, as noted above, of how to define urinary retention. None were serious; all were considered mild, and resolved on their own.

Diabetes Risk Factors

During enrollment, 516 subjects reported either a family history of diabetes or possible diabetes symptoms. A precautionary warning is included in proposed labeling describing the possibility that OAB symptoms may be indicate diabetes. Four hundred fifty four (454) subjects chose to purchase Oxytrol for Women®, but only 351 were dispensed the drug (103 were excluded for medical or administrative reasons). Most

⁹ Stanton SL, PL Dwyer, eds. 2000, Urinary Tract Infection in the Female. 1st Ed., Oxford: Blackwell Science Inc.

who received the drug actually used it (n=321). Most users (75.4%; 242/321) reported in their enrollment interviews that they did not speak to their doctors prior to use. At the EOS interviews, 293 (66.3%; 293/442) subjects who completed the interview and had previously reported diabetes risk factors reported that they had not spoken with their doctors. Of those who did speak with their doctor, nearly 70% reported that they were cleared to continue using the patch. Of those who did not, most reported that they did not feel it was necessary, that they did not have a scheduled appointment to see their doctor, or that financial constraints impacted their decisions to seek a doctor's advice.

One case of diabetes was diagnosed during the trial. A 41-year old subject (ID #12-0121) received a diagnosis two weeks after starting the drug and, on the advice of her doctor, discontinued when the diagnosis of Diabetes Mellitus Type 1 was made. She reported having OAB symptoms for five years. During the enrollment interview, she also reported heart disease, and frequent urination with excessive thirst, hunger and tiredness, but denied having any family history of diabetes. She had initially seen her doctor with a complaint of foot pain, later considered neuropathic pain due to her diabetes. She briefly restarted use after her diabetes diagnosis, but stopped due only to the cost of the product. Two other users reported blood glucose elevations detected at routine physician visits. Neither was diagnosed with diabetes.

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

Reviewer's comments: In total, only one user (0.1%; 1/785) was diagnosed with diabetes during the trial. The subject reported longstanding OAB symptoms (five years). After review of the CRF, there is no information that indicates that the diagnosis was delayed due to mis-recognition of her symptoms. In fact, the subject reported improvement of her OAB symptoms at the 3 week interview. The subject's reason for seeing her doctor (foot pain) would not likely have been self-recognized as a diabetes-related neuropathy. The excluded subject diagnosed with Type 2 diabetes also presented to her physician with an unrelated symptom (hematuria). It appears unlikely that use of Oxytrol for Women® would significantly delay diagnosis of diabetes. Diabetes is frequently asymptomatic, more often diagnosed as part of routine health, lab or urine screening. Subjects who have OAB symptoms due to early or undiagnosed diabetes would be unlikely to improve over a course of oxybutynin. Proposed label warnings to see a doctor with new or worsening symptoms, or after two weeks' use without improvement should prompt most of these consumers to seek medical

*evaluation. Also see **Section 2.6 Other Relevant Background Information** for information about the usual presenting complaints that the applicant identified in patients ultimately diagnosed with diabetes. The typical complaints seem likely and support safe use of this drug in the OTC setting.*

Bladder Cancer Risk Factors

Proposed warnings on labeling that could be consistent with a diagnosis of bladder cancer include pain and burning with urination, hematuria, flank or back pain and unexplained weight loss. In the CONTROL trial, 163 of 188 with reported symptoms chose to purchase the drug. While 56 were excluded for medical or administrative reasons, 100 subjects used the drug. Only 12 spoke with their doctor before use. No cases of bladder cancer were diagnosed during the trial, or in any subjects who had been excluded for hematuria, one of the more frequently reported symptoms preceding a diagnosis of bladder cancer.

*Reviewer's comments: This reviewer checked the reasons why subjects with hematuria chose to purchase, and wished to use the drug. Many reported that their hematuria was historical and not current, and that they were already under a doctor's care. Others considered their OAB symptoms of greater significance. Many subjects who reported hematuria saw their physicians upon exclusion from the trial. If Oxytrol for Women® is approved for OTC marketing, one would expect that, if not under a doctor's care, consumers will generally follow the labeled warning to seek medical advice if hematuria presents. Gross hematuria or previously identified microscopic hematuria are frequently disconcerting findings and Oxytrol for Women® would have no effect. See further relevant discussion in **Section 8 Postmarket Experience** under the bladder cancer subsection.*

Risk for Gastric Retention and Narrow Angle Glaucoma

There were 27 subjects who reported gastric retention after viewing the label. Twenty chose to purchase the product and used it. Seven were either excluded for medical or administrative reasons, or chose not to use the drug after purchase. All four subjects reporting narrow angle glaucoma wished to purchase the product, but were excluded from the Use phase of the trial. There were no reports of worsening gastric retention or any form of glaucoma during the use phase of the trial.

Allergic Reactions

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

Skin Reactions

There were 186 skin reactions (19.1% of all AEs) reported by 177 users (22.5%, 177/785). One report was serious, but this subject had not used the patch for nearly two months prior to diagnosis of skin blistering requiring intravenous antibiotic treatment and wound care. The blistering occurred on her buttocks where she had applied patches in the past. The most frequently reported PT was “application site irritation” (n=142) followed by “application site reaction” (n=12) and “application site erythema” (n=9). Most reports are probably related to the patch. The large majority (177/186) were mild in severity and resolved. No skin reactions worsened after patch removal. Seventy three subjects discontinued the study drug permanently due to skin AEs. Risks of skin irritation can be adequately labeled, readily self-diagnosed, and simply addressed by removing the patch from the skin.

Anticholinergic Effects

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

Anticholinergic-related events from clinical trials are seen in **Table 19**. In clinical trials to support original approval, rates of dry mouth were similar between treatment and placebo groups.

Table 19: Summary of Treatment-emergent, Anticholinergic-related AEs from Controlled Clinical Trials

Adverse Event	Placebo ^a N=249	Oxytrol® 3.9mg/d ^b N=281	All Oxytrol® ^c N=547
Dry Mouth	13 (5.2%)	21 (7.5%)	41 (7.5%)
Constipation	7 (2.8%)	7 (2.5%)	19 (3.5%)
Nausea	8 (3.2%)	5 (1.8%)	18 (3.3%)
Somnolence	1 (0.4%)	3 (1.1%)	6 (1.1%)
Dizziness	6 (2.4%)	9 (3.2%)	15 (2.7%)
Dry Eye	4 (1.6%)	2 (0.7%)	5 (0.9%)
Vision Abnormal	3 (1.2%)	5 (1.8%)	12 (2.2%)
Dysuria	1 (0.4%)	4 (1.4%)	10 (1.8%)
Palpitation	0	2 (0.7%)	4 (0.7%)
Urinary Retention	0	0	2 (0.4%)

^a Placebo subjects were administered the transdermal patch without active drug. Mean exposure = 69.7 days

^b Mean exposure in controlled periods of trials = 59.9 days

^c Doses provided 1.3, 2.6, 3.9 and 5.2 mg/d. Mean exposure in controlled periods of trials = 70.5 days

Source: Adapted from applicant's submission, Table 19, Module 5.3.5.3, Section 7.6.2.1, p. 1678.

Reviewer's comments: This table shows that rates of dry mouth were not significantly different between those subjects who received placebo and those who received any transdermal. The two urinary retention events reported with all transdermal forms were associated with an unapproved 5.2 mg/d strength. Details on higher rates of reporting of dysuria and "vision abnormal" can be found in the original NDA reviews. In the open-label extension periods of the controlled clinical trials, rates of anticholinergic-related AEs were quite low, possibly indicating tolerance to the events, mild intensity of the events or subject drop out from the extension period if AEs were too bothersome. Dry mouth and constipation are currently missing from proposed labeling, but are not uncommon and can be particularly bothersome to consumers. Warnings should be included in labeling.

Disorientation and Confusion

A total of 79 pertinent AEs were reported by 78 subjects. Preferred terms included in these AE sub-populations overlap with some included in the "anticholinergic effects" sub-population of terms. Disorientation and confusion can be considered CNS-related anticholinergic effects as well. The most frequently reported PTs were "dizziness/somnolence" (n=29), and "depression" (n=5). Two AEs were serious (schizoaffective disorder and convulsive syncope), but unlikely related to use of the study drug. Both subjects had histories of similar conditions prior to enrollment. Only one subject (difficulty chewing) permanently discontinued use of the study drug.

Falls and Accidents

In total, there were 17 subjects with 19 related AEs. Three subjects permanently discontinued the study drug. Seven were serious reports describing falls or accidents

identified in the provided list of narratives. Only three of those subjects were using the drug at the time of their incidents:

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

None of the events or narratives identified a safety signal precluding approval of Oxytrol for Women®.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In total, 519 subjects (66.1% of total users) reported at least one AE. Subjects reported 975 AEs total. The applicant considered almost 37% (n=359) possibly or probably drug-related. Over 75% of all AEs were mild in severity. **Table 20** shows the number and percentages of the most pertinent and commonly reported AEs stratified by the subjects' age. There did not appear to be any significant difference in overall AE reporting, or SAE reporting, stratified by age (< 65 years; > 65 years; > 75 years). From the subjects any each age group, 65%, 68.3% and 67% reported at least one AE, respectively. Subjects reporting SAEs made up 4%, 5.4% and 5.5% of all those in each respective age group. Of note, women < 65 reported application site irritation and constipation with greater frequency, while older subjects reported UTI, cystitis and dysuria in greater proportion.

Table 20: Frequently Reported AEs by Age (Pertinent AEs Reported by > 2% of Study Population)

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

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

Overall, in the most frequently reported System Organ Class (SOC), “Infections & Infestations” (n=212; 21.7% of total), “UTI” (n=50), “nasopharyngitis” (n=46), and “sinusitis” (n=21) were reported in more than 2% of cases. Other commonly reported SOCs included “General Disorders and Administration Site Conditions” (n=205; 21%), “Gastrointestinal Disorders” (n=119; 12.2%), “Nervous System Disorders” and “Musculoskeletal and Connective Tissue Disorders” (n=71). Only “General Disorders and Administration Site Conditions” and “Gastrointestinal Disorders” were mostly considered possibly or probably drug related, 87.3% and 58%, respectively. The other most commonly reported AEs included “application site irritation” (n=142; 14.6% of all AEs), “dry mouth” (n=32), “urge incontinence” (n=24), and “constipation” (n=20) accounting for over 2% of all reports.

*Reviewer’s comments: These reported AEs are frequently associated with anticholinergic drugs (dry mouth, constipation), transdermal drug formulations (application site reactions) and older age female subjects (UTI, urge incontinence, cystitis). There are no new safety concerns that would preclude approval of Oxytrol for Women®. See **Section 9.2 Labeling Recommendations** for discussion to include additional warnings in Drug Facts labeling based on these and the postmarketing safety reports.*

7.4.2 Laboratory Findings

See **Section 7.3.5 Submission Specific Primary Safety Concerns** for details on the overall findings from the urinalyses performed at the end of the study.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See original reviews for NDA 21351.

7.5.2 Time Dependency for Adverse Events

See original reviews for NDA 21351.

7.5.3 Drug-Demographic Interactions

Most trials conducted to support approval of NDA 21351 enrolled Caucasian females. There do not appear to be any known race differences in the incidence of common reactions associated with use of oxybutynin, application site reactions and anticholinergic-related reactions. There were no significant differences in AE reporting by age (< 65 years; ≥ 65 years).

7.5.4 Drug-Disease Interactions

Consumers with several specific disease processes should not use Oxytrol for Women® or should use it with caution. See **Figure 5: Proposed Nonprescription Label** and **Section 9.2 Labeling Recommendations**. FDA's recent postmarketing safety evaluation (see **Tracked Safety Issues** in **Section 8 Postmarket Experience**) identified dementia-related disorders, such as Alzheimer's disease, as important to consider when patients, their caretakers, and their healthcare professionals are deciding whether oxybutynin and other anticholinergic products are right for them. Due to the CNS-related effects of oxybutynin, dementia may be worsened. While safety reports were associated with oral, not transdermal oxybutynin forms, and no changes were proposed for Oxytrol®'s Rx labeling, the potential risk to older consumers seems enough to recommend that consumers over age 64 speak with their doctor prior to use.

Specifically, an Expert Panel of the American Geriatrics Society updated the Beers Criteria in 2012¹⁰. The Beers Criteria were originally established in 1991 for nursing home residents, but have since been expanded, in 1997 and 2003, to include all settings of geriatric care. The panel reviewed available evidence to advise on use or avoidance of potentially inappropriate medications for persons over age 65. Adverse drug events and other related issues were evaluated. The panel strongly recommends that patients with, or at high risk of delirium avoid use of anticholinergics, including oxybutynin, due to exacerbation of CNS effects. Patients with dementia or cognitive impairment should also avoid use of anticholinergics, including oxybutynin, due to adverse CNS effects. The strength of the evidence supporting these recommendations is moderate to high and carries additional weight because older consumers are more likely taking multiple, potentially interacting medications for comorbid conditions. Additionally, patients with chronic constipation are recommended to avoid use of oral oxybutynin if possible. In consumers over age 65, and in the clinical situations described, oxybutynin is considered to have risks that outweigh the benefits. Another tool to screen for potential risk associated with drug use in older consumers are the **Screening Tool for Older Persons' Prescriptions (STOPP)**, and the **Screening Tool to Alert doctors to Right Treatment (START)**¹¹. The STOPP criteria state that

10 The American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012, American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, *J Am Geriatr Soc*, 60: 616-631.

11 Gallagher P, C Ryan, S Byrne, J Kennedy, D O'Mahoney, 2008, STOPP (Screening Tool of Older

antimuscarinic drugs for urinary indications should not be used by patients with dementia, chronic glaucoma, chronic constipation or chronic prostatism.

Reviewer's comments: As noted elsewhere, over 45% of subjects in clinical trials to support original approval were over age 65. There were no differences in AE reporting by age. Also, the postmarketing data does not identify any related safety signals that would preclude OTC availability. However, this reviewer recommends that OTC labeling instruct consumers 65 years of age or older to speak with their doctors prior to use of oxybutynin. The criteria also support including warnings about constipation and concomitant use of other anticholinergic drugs.

7.5.5 Drug-Drug Interactions

The Rx label for Oxytrol® warns against concomitant use with other anticholinergics or drugs that may cause anticholinergic-like effects such as dry mouth, constipation, etc. While no specific drug-drug interaction studies were conducted to support approval of NDA 21351, the label warns that oxybutynin may theoretically affect gastrointestinal motility, thereby potentially affecting absorption of oral medications. See **Sections 4.4.3 Pharmacokinetics** and **9.2 Labeling Recommendations** for further details on possible drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There has been no formal evaluation since there were no non-clinical signals in studies of oral formulations completed to support approval of NDA 21351. See **Section 4.3 Preclinical Pharmacology/Toxicology** for further information on the evaluation of dermal carcinogenicity.

7.6.2 Human Reproduction and Pregnancy Data

The Rx label states that there are no adequate and well-controlled studies using Oxytrol in pregnant women. Nonclinical data supports a lack of harmful effects on fertility or fetal development. The proposed drug label indicates that women who are pregnant, or who may be pregnant, should speak to their doctor before use. Early pregnancy may cause symptoms also consistent with idiopathic OAB; however, such patients would not benefit from use of Oxytrol for Women® and would only increase their risk associated with use. See Ms. Barbara Cohen's review for details on label comprehension and self-selection for use of Oxytrol for Women® by pregnant women. See also the **Pregnancy**

Person's Prescriptions) and START (Screening Tool to Alert Doctors to Right Treatment). Consensus Validation, *Int J Clin Pharmacol Ther*, 46: 72-83.

subsection of the section *Safety Topics of Special Interest* in **Section 8 Postmarket Experience** for further details.

7.6.3 Pediatrics and Assessment of Effects on Growth

The proposed Rx-to-OTC switch does not include any changes to the active ingredient, the indication, the dosage form, dosage regimen or route of administration. As per PREA (21 U.S.C. 355c), there does not appear to be a reason to require a pediatric development plan or proposals for waivers or deferrals. The target population will be considered as proposed, women over age 18.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There are limited data pertinent to using more than one patch of Oxytrol at a time. (See Section 8). There are no reports of patch ingestion in AERS, or in the AAPCC database (see **Section 8 Postmarket Experience**). The bioavailability of oxybutynin after ingestion of a patch is unknown. See **Section 9.1 Literature Review/References** for details of sporadic cases of abuse of oral forms for the CNS-related anticholinergic effects. According to Rx labeling, overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmias, vomiting, and urinary retention.

7.7 Additional Submissions / Safety Issues

Because this is an Rx-to-OTC switch of the same dosage strength and regimen for female consumers, the applicant submitted pooled safety data from clinical efficacy trials to support approval of the original application, NDA 21351. Data were pooled from two phase 3 trials and a dose-ranging, phase 2 trial (see **Table 5**). The mean age of trial subjects was 62 years, with 46% over age 65. Duration of exposure at doses up to 5.2 mg/day (1.3 times the proposed OTC dose) ranged from 1-428 days with subjects exposed to the proposed OTC dose, 3.9mg/day, for an average of 97 days (0-387 days). Within all studies conducted to support approval of the original NDA, 663 symptomatic subjects and 83 healthy volunteers received at least one dose of an oxybutynin patch. Subjects were exposed to drug for an average of 151 days, or 37-50 patches based on the proposed 3-4 day dosing regimen.

Reports of AEs (see **Table 21**) were more frequent in active (73%) compared to placebo (57%) groups and also more frequent with increasing dosage strength. There were 1867 AEs reported by all subjects receiving oxybutynin in clinical trials. Most (68.8%) were considered unrelated to treatment. The most common events were related to application-site reactions and dry mouth. In total, application site reactions were almost twice as frequently reported in the treatment groups (23%) over placebo groups possibly indicative of irritation as a direct result of oxybutynin exposure. Dry mouth, like other anticholinergic-related AEs, was reported by subjects in treatment

groups slightly more often than by those receiving placebo (8.6% versus 5.4%). SAEs accounted for 47 of the total. None were considered drug-related. Nine subjects discontinued due to an SAE. See Dr. Gierhart's and Dr. Batra's clinical reviews for further details.

Table 21: Total AEs and Treatment-related AEs in >2% of Subjects in Controlled Clinical Trials for NDA 21351 (Oxybutynin Patches Versus Placebo Patches)

Preferred Term	Oxybutynin Transdermal (all dose strengths) N=547	Placebo Transdermal N=249
	Total AEs	Total AEs
Application site pruritis	74 (13.5%)	13 (5.2%)
Mouth dry	41 (7.5%)	13 (5.2%)
Application site erythema	28 (5.1%)	6 (2.4%)
Diarrhea	25 (4.6%)	14 (5.6%)
Inflicted injury	21 (3.8%)	7 (2.8%)
Rhinitis	21 (3.8%)	9 (3.6%)
Headache	20 (3.7%)	7 (2.8%)
Constipation	19 (3.5%)	7 (2.8%)
Nausea	18 (3.3%)	8 (3.2%)
Urinary tract infection	17 (3.1%)	11 (4.4%)
Sinusitis	17 (3.1%)	4 (1.6%)
Dizziness	15 (2.7%)	6 (2.4%)
Myalgia	15 (2.7%)	2 (0.8%)
Back pain	15 (2.7%)	8 (3.2%)

Source: Adapted from applicant's submission, Table 2, Module 5.3.5.3, Section 2.3.2, p. 14.

Reviewer's comments: AEs reported in uncontrolled and open-label extension trials were generally similar to those above. However, UTI was reported in over 10% of subjects in those trials.

Overall, 13.7% of subjects discontinued trials due to AEs. Discontinuations due to application site reactions were more common, and more likely in the treatment groups, particularly in those groups administered higher dose strengths. No deaths occurred during any trial.

8 Postmarket Experience

Oxytrol® has been marketed in the U.S. since June 2003. It has also been marketed worldwide in several countries for several years. Twenty six periodic safety reports have been submitted since marketing began. FDA has also conducted three postmarketing safety assessments (tracked safety issues) with implications for anticholinergic drug products, including Oxytrol®.

The applicant estimates that nearly (b) (4) patches have been sold in the U.S. since market launch in 2004 through February 2012. Worldwide, over (b) (4) patches

have been sold. Based on use of two patches per week, this equates to about 53,000 patient-years of exposure. Over two years of Gelnique® marketing, over (b) (4) doses have been sold. With daily use, this equates to about 9,000 patient-years of exposure.

Tracked Safety Issues

In 2006, FDA initiated a safety review to evaluate anticholinergics, indicated for relief of OAB symptoms, alone and when used concomitantly with cholinesterase inhibitors. Interactions were implicated in reports of central nervous system (CNS) adverse events, including worsening dementia. Theoretically, efficacy of cholinesterase inhibitors may be decreased by concomitant use of anticholinergics leading to aggravation of dementia symptoms in those patients undergoing treatment for diseases such as Alzheimer's disease. The degree of effect may depend on the permeability of the blood-brain barrier to the drug since there are several different drugs indicated for treatment of OAB symptoms. On their own, anticholinergics may also contribute to worsening dementia symptoms in susceptible, often elderly, patients who are more likely to suffer OAB symptoms as well.

While there is wording in the Oxytrol® Rx label about disorientation or memory loss with overdosage, there are no precautions or warnings for interactions with cholinesterase inhibitors. Further, there are limited labeling identifying CNS side effects. Safety evaluators gathered 353 cases of patients using anticholinergic drugs and reporting confusion, dementia and delusion, for example. Of those cases, 102 identified oxybutynin. Thirteen oxybutynin cases reported history of dementia/ Alzheimer's disease. Two reported also taking cholinesterase inhibitors. Four (4%) of the total reports (102) further identified Oxytrol® as the primary suspect drug, and identified memory impairment (3) and disorientation (1). For reference, the reviewer utilized available resources to project over (b) (4) new or refill prescriptions of Oxytrol® per year for 2003-2005. Reviewers from the Division of Drug Risk Evaluation in the Office of Surveillance and Epidemiology (OSE) proposed the following revisions of labeling:

'PRECAUTIONS:

- *Anticholinergic medications such as (insert drug name) have the potential to cause anticholinergic CNS effects (e.g., confusion, hallucinations, memory impairment, cognitive impairment), particularly in patients who are susceptible to cholinergic deficits (i.e., dementia patients and the elderly).*
- *Anticholinergic medications such as (insert drug name) should be used with caution in patients with preexisting dementia treated with cholinesterase inhibitors because of opposing pharmacological action and risk of aggravation of symptoms.*
- *Patients who are susceptible to cholinergic deficits (i.e., dementia patients and the elderly) should be monitored for signs of anticholinergic CNS effects including aggravation of dementia, particularly in the first month after beginning treatment or*

increasing the dose. If patients experience anticholinergic CNS effects, drug discontinuation should be considered.

According to the Division of Reproductive and Urologic Drugs (DRUP), the data were insufficient to support a class precaution for all anticholinergic drugs used concomitantly with cholinesterase inhibitors or by patients with dementia-related diseases. DRUP recommended certain drug-specific labeling changes to support safe use:

- Add new precautions for patients with preexisting dementia who use both drugs and may be at risk for aggravation of symptoms.
- Add certain AEs under various subheadings listing CNS reports.
- Wording similar to the 3rd bullet, above, under **PRECAUTIONS**.

*Reviewer's comments: No labeling supplement to reflect these proposals was ever requested of the Oxytrol® NDA holder, or submitted by them. The reason is because pertinent AEs were not reported for transdermal forms of oxybutynin, and the safety profiles between oral and transdermal forms differ. See **Section 9.2 Labeling Recommendations** for comments.*

In 2010, FDA initiated a safety assessment to review cases citing “disturbances in consciousness,” including somnolence, and reports of accidents or injuries associated with use of antimuscarinics, including oxybutynin drug products. This review was prompted by a proposal by one NDA holder to add “somnolence” to the postmarketing surveillance section of their drug’s label. Somnolence may result in motor vehicle accidents, or other accidental and avoidable injuries. NDA holders were asked to provide somnolence and somnolence-related cases from their pharmacovigilance databases for FDA review. A DRUP review of Oxytrol® was completed on June 11, 2012. An AERS search identified 31 somnolence-related cases associated with all forms of oxybutynin. The Oxytrol® NDA holder identified 203 unique cases in their database, of which 25 were considered serious.

Eleven of 25 serious cases reported disturbances in consciousness. No consequent accidents or serious injuries were reported. Interesting cases include:

- Case #2005-01306 (U.S.): 89 year old female experienced an overdose two days after applying two patches simultaneously on the advice of her doctor. She had symptoms of disorientation, aphasia, depressed level of consciousness, trismus and dysarthria. The patient was being monitored for seizure activity and evaluated for a psychiatric disorder.
- Case #2006-01393 (U.S.): 87 year old female became lethargic and disoriented following three days of use of Oxytrol®. Symptoms improved after patch was discontinued (along with other unidentified concomitant drugs). Patient’s medical chart noted that symptoms were “due to Oxytrol®.”

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As part of the search, the applicant reported 169 cases of somnolence (83%) related to use of transdermal formulations. Five cases were serious and one included report of a serious injury. Forty nine cases reported concomitant medications where drowsiness is a known adverse reaction. Two examples are described:

- Case # 2008-00301 (U.S.): 60 year old female, with no medical history reported, was hospitalized with confusion and somnolence following a likely fall after applying an initial dose of Oxytrol®. Her medical evaluation was normal. Hospital diagnosis was recorded as “possible drug reaction with Oxytrol®.” She had also been taking trazodone and clonazepam which are known to cause drowsiness; however, the temporal relationship to use of oxybutynin and the improvement of symptoms following removal of the patch supported causality.
- Case #2004-01863 (U.S.): 73 year old male with history of Parkinson’s disease reported drowsiness and fatigue the morning after applying an Oxytrol® patch. Events subsided after patch removal.

Reviewers in DRUP concluded that the reports indicate that Oxytrol® users may be at risk for accidents or injury if the drug is used prior to driving or operating machinery. Therefore, they recommended the NDA holder submit a supplemental application to revise labeling. The **WARNINGS AND PRECAUTIONS** section of the Rx label would include the term “somnolence” under a new Central Nervous System Effects subsection with advice not to drive or operate machinery until the effects of oxybutynin are known to the patient.

*Reviewer’s comments: See **Section 9.2 Labeling Recommendations** for comments on proposed labeling.*

In 2011, FDA initiated a safety review of angioedema cases associated with use of antimuscarinics, such as oxybutynin. Two oral formulations were linked with increased risk of angioedema. While serious cases of angioedema, anaphylaxis and urticaria were identified with use of oral oxybutynin formulations, none identified transdermal formulations of oxybutynin, or Oxytrol® in particular. Labeling for oxybutynin drugs did not mention angioedema or anaphylaxis. In order to adequately advise patients and healthcare professionals of serious reactions, OSE recommended the addition of label warnings for angioedema and anaphylaxis for all oxybutynin drug products. Subsequently, reviewers from DRUP recommended the following labeling changes, where indicated, to oral anticholinergic drugs indicated for management of OAB symptoms:

- A new **WARNINGS AND PRECAUTIONS** section that identifies signs and symptoms of angioedema and recommends airway management.
- A new ‘Information for Patients’ subsection of the **PRECAUTIONS** section with similar statements as above.
- New listings to the **ADVERSE REACTIONS** section and supplemental patient material including related postmarketing AEs.

DRUP reviewers believed that reports identifying transdermal oxybutynin formulations (Oxytrol® and Gelnique®) did not support significant changes to the warnings sections of the labels. There were few reports in light of the large number of doses distributed over several years. Specific to Oxytrol®, DRUP performed a search of the AERS database in April 2010 finding only two possible cases of angioedema. Both were considered nonserious:

- 78 year old female with facial “angioneurotic edema, unilateral and with fever.” There was no airway involvement. The patient had been using transdermal oxybutynin (not further identified). Symptoms resolved after stopping use and beginning a course of prednisone.
- 40 year old female patient’s spouse reported a progressive rash with hives after using Oxytrol® for over two weeks. The patient also had edema. Treatment included steroids, Benadryl®, epinephrine, Tagamet® and an unidentified injectable drug.

Neither Oxytrol® nor Gelnique® labels list “angioedema” or “anaphylaxis” as AEs. Ultimately, however, DRUP was concerned about the potential seriousness of airway obstruction resulting from angioedema and felt that individualized warnings should be made in labeling for all antimuscarinic products. For Oxytrol®, they recommended (October 19, 2010) that the NDA holder makes the following labeling changes:

- Create a new **WARNINGS AND PRECAUTIONS** section to state “[A]ngioedema requiring hospitalization and emergency medical treatment has occurred with the first or subsequent doses of oral oxybutynin. In the event of angioedema, Oxytrol® should be discontinued and appropriate therapy promptly provided.
- “Information for Patients” should include “Patients should be informed that angioedema has been reported with oral oxybutynin use. Patients should be advised to promptly discontinue oxybutynin therapy and seek immediate medical attention if they experience symptoms consistent with angioedema.”

Postmarketing Safety Studies and Adverse Event Reporting

OSE Consultations

The Office of Surveillance and Epidemiology was asked to conduct a search for AERS reports of “significant skin irritation” and “skin cancer” based on the lack of data on risk for dermal carcinogenicity (see **Section 4.3 Preclinical Pharmacology/Toxicology**). Carolyn Volpe in the Division of Pharmacovigilance conducted a search beginning on the day of approval, February 26, 2003, through June 6, 2012 for the following search terms:

- All Preferred Terms (PT)
- Skin and subcutaneous tissue disorders – System Organ Class (SOC)
- Administration site reactions, application and installation site reactions, chemical injuries, thermal burns – High Level Terms (HLT)

- Skin neoplasms, malignant and unspecified, and skin premalignant disorders – Standard MedDRA Queries (SMQ)

There were 121 total AERS reports identified that met search criteria. Of these, 106 were serious including 57 hospitalizations. There were 23 “significant skin irritation” reports. Of these, 17 were serious including 11 hospitalizations. Some of these reports may be duplicates or the events may not be related to oxybutynin use. There were no skin cancer reports.

Reviewer’s comments: The demographic information submitted with the above OSE review noted several hospitalizations for seemingly innocuous events such as “application site erythema,” “dry skin,” or “application site pruritis.” I evaluated a sampling of these reports further. Frequently, Oxytrol® was not the primary suspect drug linked to the reasons for hospitalization, which were often unrelated to any skin disorders.

Postmarketing Safety Trial

The applicant provided safety data from a completed (2004-5) phase 4 **MATRIX** trial (**M**ulticenter **A**ssessment of **T**ransdermal Therapy in Overactive Bladder with **O**xybutynin TDS; Protocol OXY0402) conducted by the NDA holder. The trial evaluated health related Quality of Life (QoL) measures, work productivity, depression, treatment satisfaction and persistence in a large community-based population (n=2881). The trial also provided data on safety, tolerability and product use. Subjects had OAB symptoms, determined by a physician, who then provided a prescription for monotherapy with Oxytrol®. These subjects may have been dissatisfied with their current treatment, wished to try a different route of administration or were previously untreated. Nearly 75% reported that their OAB symptoms affected their lives “a lot.” Subjects needed only one symptom to participate, either urge incontinence, urgency or increased frequency. The trial was conducted in a naturalistic setting with minimal interaction between subjects and trial personnel.

Reviewer’s comments: This reviewer will only comment on the safety data collected and analyzed in this trial. It is assumed that each subject’s physician determined that the drug was appropriate for use. FDA has previously stated that this trial would not support effectiveness in the OTC setting. A final study report was never submitted for review under the original NDA.

Subjects received a one-month supply of Oxytrol® with instructions for use. No subject could have ever used Oxytrol® previously. Re-supply and follow up visits occurred at the one, three and six month marks when AEs were also recorded.

One cohort received additional educational supplement materials, while the other received only ordinary care. Most patients were female (87%) with a skew towards older age (median 63 years of age). Only half (49%) of the subjects completed all six months of treatment. The most common reasons for early discontinuation were AEs (22% overall), consent withdrawn (7.9% overall) and lost to follow up (7.5%). Discontinuation due to AEs occurred most frequently for skin irritation or dry mouth.

The safety population included all subjects who received at least one dose of test drug. A total of 2834 AEs were reported by 1328 patients (46%). Over 50% were considered drug-related by the investigators. The most frequently reported AEs were in the SOCs General Disorders & Administration Site Conditions and Skin & Subcutaneous Disorders, accounting for nearly 40% of all AEs (n=1129). The events reported included mostly skin irritation-related conditions, i.e., “application site pruritis” (n=142; 4.9%), “application site erythema” (n=131; 4.5%) and “application site dermatitis” (n=129; 4.5%). Subgroup analysis by gender or age (< 65 years or ≥ 65 years) did not identify any differences, except that older subjects tended to report more skin (11.6% versus 10.4%) and gastrointestinal AEs (10.7% versus 8.2%). “Dry mouth” (n=84) was the most common anticholinergic-related event. Other anticholinergic-related events were “constipation” (n=58), “dizziness” (n=56) and “blurred vision” (n=36). Skin irritation events and dry mouth were the only AEs reported by > 2% of the trial population. “Urinary tract infection” was identified in 82 cases reported by 67 patients (three had UTIs diagnosed and treated at enrollment; nine had multiple UTIs), but the trial sponsor only considered one case related to drug treatment. Five cases were serious and nine discontinued the trial, though four of those restarted after the UTI was treated.

Reviewer’s comments: The applicant’s report of this trial does not include details of subjects’ pre-enrollment symptoms, or address if some subjects may have had symptoms more consistent with early UTI than idiopathic OAB; although, subjects with untreated UTIs were excluded from enrollment. It is notable that 10 subjects had UTIs diagnosed within the first week after starting test drug. Only one discontinued the trial due to UTI. Since no further narratives regarding the subjects’ pre-enrollment history of symptoms were provided in the report, it is difficult to assess whether the subjects’ initial OAB symptoms may have been due to undiagnosed UTI. Sand, et al.¹ noted that most subjects in the trial had OAB symptoms for over two years (69.5%). They reported only 12% of subjects had symptoms for < 1 year, but do not further define symptom duration.

Reports of serious AEs were skewed towards older patients. In those > 65 years of age, 5.5% of subjects reported SAEs compared to only 2% of those under 65. However, older subjects had more comorbidities that could increase their risk of serious events. Also, older subjects were not more likely to discontinue the trial due to AEs. The most commonly reported SOC for SAEs was “infections and infestations” (n=28) where “pneumonia” (n=8) and UTI (n=5) were most often reported. Preferred terms under “Nervous System Disorders” (n=26) and “Cardiac Disorders” (n=20) were also more frequently reported, particularly “cerebrovascular accident” (n=7), “dizziness” (n=5) and “myocardial infarction” (n=7), respectively. There were three deaths, two from cardiovascular causes and one from natural causes, all unrelated to drug.

Reviewer’s comments: Overall, the frequently reported AEs appear consistent with those included in Rx labeling and proposed OTC labeling, skin irritation and anticholinergic effects. Drug relatedness was not clearly defined and reports of UTI seemed high, but the median older age of this population may increase the risk of UTI.

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

There were nine diabetes-related adverse events, e.g. hyperglycemia, other complications from pre-existing diabetes, but none were new diagnoses, and none led to discontinuation. No pregnant subjects were enrolled in the trial, and there were no new pregnancies reported. There were 16 reports of falls leading to fractures and other injuries, though none were considered drug-related by the investigator. Another patient reported BPH nearly four months into the trial. He was diagnosed with prostate cancer three weeks later.

Adverse Event Database Reporting

The applicant submitted a comprehensive postmarketing AE report for the Rx Oxytrol® drug product. The report included the following:

- Summary of International Postmarketing Safety Update Reports (PSURs) and Periodic Adverse Drug Event Reports (PADERs) from the NDA holder, Watson Pharmaceuticals, Inc. – **June 2003 (market launch) - February 25, 2012**
- Review of postmarketing safety from AERS (**January 1, 2003 – December 31, 2011**), WHO (**January 1, 2003 – April 30, 2012**), American Association of Poison Control Centers (AAPCC) databases (**February 1, 2003 – April 30, 2012**)
 - Focused review of topics of special interest
 - Diabetes
 - Urinary tract infection (UTI) and bladder cancer
 - Pregnancy
 - Skin reactions
 - Anticholinergic AEs
 - Urinary retention
 - Narrow angle glaucoma
 - Falls, disorientation, confusion

Reviewer's comments: Drug Abuse Warning Network (DAWN) data was not submitted as the database is undergoing transformation.

- Review of the scientific literature pertinent to safe use in the Rx setting (**1996 - April 2012**). See **Section 9.1 Literature Review/References**.
- The 120-day safety update was submitted on July 27, 2012. It included updates from the NDA holder's pharmacovigilance database for Oxytrol® and Gelnique®, AERS, WHO, AAPCC and new reports from the scientific literature. No new clinical trials were undertaken or completed.

PSUR/PADER Review

The product has been marketed in several foreign countries since August 2004. Nearly 9700 and 3750 reports, respectively, have been included in the PADERS and PSURs since marketing began inside and outside the U.S. At the pre-NDA meeting between FDA and the applicant, FDA asked for a rationale to support the NDA with postmarketing safety data from only the transdermal forms of oxybutynin. MCC offered several reasons to support adequacy of the data:

- Regarding AEs, transdermal formulations compared similarly to placebo in clinical trials.
- Transdermal formulations bypass first-pass metabolism, reducing formation of NDEO which is believed to be more significantly associated with anticholinergic-related AEs. MCC believes this separates the safety profiles of transdermal versus oral forms of oxybutynin. They report that saliva production is also preserved to a greater degree

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with transdermal versus oral forms thus limiting complaints of anticholinergic-related dry mouth.

- In 74 subjects who completed a trial comparing tolerability of oral versus transdermal forms of oxybutynin, the safety profile with transdermal use was better, particularly for dry mouth events (38% versus 94%, $p=0.001$). These subjects had previously been treated with oral oxybutynin. Anticholinergic-related events, overall, were reported less frequently in the transdermal group¹². Only 13% of those treated with either placebo or test drug patches reported more than mild skin erythema.
- Safety data from clinical trials supporting original approval of the Rx NDA show lower rates of anticholinergic side effects with use of transdermal oxybutynin compared with rates seen historically in trials for oral oxybutynin.
 - Dry mouth was most frequently reported, but at a rate much lower than that from use of oral forms (7.5% versus 57.9%). Constipation and nausea were reported next most frequently, but much less often with transdermal use. The caveat, however, is that these comparisons were across trials and historical.

Reviewer's comments: Reviewers from DRUP agree that it is reasonable to review only postmarketing safety data from use of transdermal forms of oxybutynin. Several special safety topics will be addressed separately.

The applicant notes that nearly (b) (4) patches have been distributed in the U.S. since 2003; about (b) (4) worldwide. In all, 13,190 AEs (96%) were classified as non-serious. While 595 AEs (4%) were considered serious, only 106 were labeled events. Dizziness, somnolence and angioedema are the only AEs warranting labeling changes since original approval. Angioedema has only been reported with use of oral forms, but was included on the Oxytrol label due to its seriousness.

Over 32% of all AEs included reports of "application site erythema," "application site pruritis," or ineffectiveness. Over 5300 AEs (40%) described application site-related terms. In the PADERS, gastrointestinal disorders accounted for 11.5% of all reported AEs, with "dry mouth" ($n=311$; 3.1%) most frequently reported. This was the most common anticholinergic side effect and included in 99 (2.6%) reports within PSURs. Other possible and frequent anticholinergic effects included "constipation" ($n=222$), "blurred vision" ($n=252$), "dizziness" ($n=247$) and "somnolence" ($n=207$). Nervous System disorders account for 7.7% of all reported AEs in PADERS, with dizziness-related events most common, followed by "fatigue." Only 8 AEs were reported in more than 2% of cases submitted in PADERS (**Table 22**). No additional significant preferred terms were identified.

12 Davila GW, CA Daugherty, SW Sanders, 2001, A Short-term, Multicenter, Randomized Double-Blind Dose Titration Study of the Efficacy and Anticholinergic Side Effects of Transdermal Compared to Immediate Release Oral Oxybutynin Treatment of Patients with Urge Urinary Incontinence, *J Urol*, 166: 140-145.

*Reviewer’s comments: Reports from PSURs are combined from various international drug safety monitoring authorities. The number of reports may be overestimated due to duplication. Comments on the impact of these reported events, particularly application site reactions, anticholinergic effects and drug ineffectiveness will be addressed in the section on “AERS Reports.” Dry mouth and constipation are common anticholinergic effects of oxybutynin use and both should be listed on the OTC Drug Facts label (see **Section 9.2 Labeling Recommendations**). The frequent reporting of application site reactions, and even drug ineffectiveness, can be addressed quite readily by consumers in the OTC setting. They may consider removing the patch and choosing an alternative drug.*

Table 22: AEs Reported in PADERS with Frequency \geq 2%

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

Source: Adapted from Table 13, p. 74 of Module 5, Integrated Summary of Safety, Section 3.5.2.1

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

This reviewer performed a focused AERS search on AEs that may be associated with falls or injuries, particularly in older patients, i.e., “vision blurred,” “dizziness,”

“somnolence,” “fatigue,” “confusional state,” and “asthenia.” I was concerned about some of the cases from the NDA holder’s database. I identified three SMQs (Standardized MedDRA Queries) that contain the above preferred terms plus others that may be associated with falls or injuries, “accidents & injuries,” “vestibular disorders,” and “hypotonic-hyporesponsive episode.” I searched these terms in reports (February 2003 through July 2012) identifying Oxytrol®, Gelnique® or transdermal patches not otherwise specified. There were 29 cases in total. Upon review, a sampling of cases follows:

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

*Reviewer’s comments: This reviewer did not find any new safety signals based on review of the SAE narratives provided by the applicant. There were a few cases reporting injuries related to falls, but most of those reports did not include enough information to determine whether Oxytrol® use could be implicated. The reports also frequently list comorbidities with fall risks, e.g., neuropathies, joint replacements, vertigo, and concomitant medications that could be suspect, including clonazepam and zopiclone (not approved in the U.S.). These reports identified mostly elderly patients (average age=69 years (44-89)) who are at risk for falls for myriad reasons separate from use of Oxytrol®. However, in concert with reports of dizziness, somnolence and confusion, risk of falls is a concern. See **Section 9.2 Labeling Recommendations**.*

The applicant provided postmarketing safety data for Gelnique® as well. It was approved in 2009 for the same indication in a topical gel formulation. Two PSURs have been submitted. Almost 1950 AEs have been reported for Gelnique® which has total distribution of over (b) (4) doses in the U.S. The findings are very similar to those

reported with use of Oxytrol®, although reports of application site reactions are more common with Oxytrol®.

AERS Database

The FDA-AERS database contains spontaneous reports of AEs from a variety of sources and there is considerable overlap between the data contained in AERS and the PSUR/PADER data. Interpretation of spontaneously reported AEs has several limitations:

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

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

A total of 4279 AEs, identifying all forms of oxybutynin as suspect, are included in AERS. The applicant excluded cases listing oxybutynin as concomitant with no relation to the reported event. This reviewer focused the review on the Oxytrol® patch, Gelnique® topical gel, or reports indicating use of an unidentified transdermal patch. In total, there were 604 AEs associated with use of Oxytrol®. There were 116 AEs in reports identifying use of Gelnique®, and 81 cases reporting use of an unidentified oxybutynin transdermal drug product. Over 72% of all cases involve female patients. For Gelnique®, there were 10 SAEs reported in children 2-5 years of age for which the drug is not indicated. No further information on these cases was provided by the applicant.

Reviewer's comments: The applicant included AE data identifying oral forms of oxybutynin and oxybutynin not otherwise specified (NOS). The frequently reported events are common to all oxybutynin drug products. For skin-related AEs, only "rash" was reported more than 1% of the time; therefore, making it unlikely that transdermals were used to great degree. Because this reviewer accepts that the safety profiles between oral and transdermal forms are different, and it is not possible to distinguish formulations in the NOS reports, I will focus only on the identified transdermal forms.

The most frequently reported SOCs were General and Administration Site disorders (n=140; 21%), Psychiatric disorders (n=81; 12%), Nervous System disorders (n=81;

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12%) and Gastrointestinal disorders (n=53; 8%). Events accounting for more than 2% of all reports include only “drug ineffective” (n=29), “pharmaceutical product complaint” (n=13) and “application site erythema” (n=11). Other frequent, possibly oxybutynin-specific events, include “dry mouth,” “application site pruritis,” “dizziness,” “constipation,” “urinary tract infection,” and “vision blurred.” Most of these were reported 6-10 times each (1%). Application site reactions accounted for about 40% of all PTs under General and Administration site disorders.

Reviewer’s comments: The reported events are consistent with those included in the NDA holder’s database. In those cases where age was reported, patients >65 years of age accounted for 42% of the reported events. They account for 58% if cases without age reported are excluded. Skew towards older age supports proposed labeling revisions warning consumers that some of the anticholinergic and nervous system-related side effects may put people at risk for injuries from falls, driving or operating heavy machinery.

Interestingly, 92% of the total number of AEs for transdermals are classified as serious (N=690), in stark contrast to reports in the NDA holder’s database (see subsection on PADER/PSUR review above), mostly classified as non-serious. The most frequently reported SAEs (10 or more reports, or >1.7%) were drug ineffective, pharmaceutical product complaint, application site erythema, fall. Nine others including dizziness and vision blurred were also more commonly reported.

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

WHO Database

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

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

The most frequently reported SOCs include General Disorders and Administration Site Conditions (n=102, 34%) followed by Skin and Subcutaneous Tissue Disorders and Gastrointestinal Disorders, 35 (13.6%) and 31 (12.1%) AEs respectively. Individual AEs that accounted for $\geq 2\%$ (five or more) of the total include “drug ineffective” (n=36), “application site reaction” (n=12), “rash” (n=8), “nausea” (n=6), and “application site erythema,” “dizziness,” and “pruritis” (n=5 each). Other, anticholinergic-related events included “dry mouth” (n=4), “vision blurred” (n=3), and “somnolence,” “fatigue” or “sedation” (n=7). Additionally, there were several reports (n=8) that indicate falls or increased risk for falls, i.e., “fall,” “muscular weakness,” “gait disturbance,” “accident at home,” “spinal fracture,” or “disorientation.” Of the total, 115 events (37.7%) were considered serious. General Disorders and Administration Site Conditions and “application site erythema” were the most frequently reported SOC and PT, respectively.

Reviewer’s comments: Overall, the frequently reported AEs are consistent with known risks associated with proposed OTC use of Oxytrol for Women®. In the context of distribution and sale since worldwide marketing began, the number and seriousness of AEs do not appear significant. There are no new safety signals identified. The important risks can be included in labeling to support safe and proper use of the drug.

AAPCC Database

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

Safety Topics of Special Interest

There are several medical conditions and diseases that may share urinary symptoms with idiopathic OAB. The applicant’s consumer behavior evaluation attempted to determine whether consumers, who may have symptoms of such conditions or diseases, will appropriately choose to speak with their doctor first, or not select to use the drug. An inappropriate selection decision may delay diagnosis and treatment of a serious medical condition. Additionally, consumers may use Oxytrol for Women® when they are unlikely to benefit from its use, thereby exposing themselves to risks associated with transdermals and anticholinergic drugs. However, it is important to note that consumers with these conditions may also have unrelated OAB symptoms and,

therefore, may benefit from use of oxybutynin. Also, since consumers with these conditions are unlikely to have sustained improvement in their symptoms, they are likely to stop use and see their doctor, as directed on the proposed OTC label.

This section of the review will focus on pre-approval and postmarketing reports identifying diagnoses of diabetes mellitus, UTI, bladder cancer and pregnancy. It will include further evaluation of reports of anticholinergic effects, urinary retention, and narrow angle glaucoma and address reports of falls, confusion and disorientation. Data from the CONTROL AUS will be addressed in **Section 7 Review of Safety**. In the applicant's retrospective medical record review, Protocol CL2010-08, patients age 18-85, with an initial diagnosis of diabetes, UTI or bladder cancer, were assessed as to whether they presented with urinary symptoms also consistent with OAB. The objective was to determine the incidence of presentation of urinary symptoms leading to diagnosis of diabetes, UTI or bladder cancer. Medical records from four sites were reviewed for ICD-9 diagnostic codes for initial and primary diagnosis of diabetes, UTI or bladder cancer.

*Reviewer's comments: Data from the retrospective chart review is evaluated in **Section 2.6 Other Relevant Background Information**.*

Diabetes Mellitus

Type 2 diabetes accounts for an overwhelming percentage of the number of patients diagnosed with diabetes (and surely those undiagnosed) in the U.S. The prevalence of diabetes, and pre-diabetes, increases with age. Some consumers with diabetes may have increased urinary frequency and increased thirst. Others may have a more insidious, initially asymptomatic onset that may go undiagnosed for many years. Increased urinary frequency (polyuria) in diabetes is due to increased urinary volume. Oxybutynin is unlikely to have any effect since OAB symptoms are due to bladder detrusor muscle instability and not hypervolemia. Since there is unlikely to be any benefit, it is important to determine whether there is a potential risk for delayed diagnosis of diabetes, with use of the drug, in consumers who have urinary symptoms associated with the disease. The applicant proposes an OTC label warning to address this issue.

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

Reviewer's comments: Onset of symptoms due to diabetes is often insidious. Based on the data evaluated in this review, consumers with OAB symptoms appear unlikely to

have a diagnosis of diabetes delayed, by any significant extent, due to the availability of Oxytrol for Women® in the OTC marketplace.

Bladder Cancer

Bladder cancer, although relatively uncommon (21 new cases per 100,000 per year), occurs more often in older persons and in males (2.7:1). Symptoms of urinary frequency or urgency may occur based on the location and size of tumors. More often, hematuria, particularly painless and gross, is a presenting sign in patients with bladder cancer. Symptoms similar to UTI may also present initially, and unsuccessful antibiotic treatment of UTI is a common first intervention before cancer is diagnosed. **Table 23** compares presenting symptoms among diagnoses that can mimic OAB.

Table 23: Comparison of Presenting Symptoms for OAB, Bladder Cancer and UTI

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

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

Reviewer's comments: The symptoms relatable to bladder cancer appear to differ significantly enough from OAB to support minimal risk of delay in diagnosis, although, oxybutynin may have a temporary effect on OAB symptoms due to bladder cancer, particularly early, or in situ, cancer.

There were no bladder cancer cases identified in clinical trials conducted to support original approval, or in postmarketing clinical trials. There was one case of bladder cancer identified in AERS coincident with use of transdermal oxybutynin. The report did not state whether the diagnosis appeared delayed due to use of the drug.

In the literature, Månsson et. al.¹³ analyzed the reasons for diagnostic delays in 343 bladder cancer patients in Sweden. According to the authors, diagnosis often depends on the patient's and primary physician's response to early signs and symptoms. There were significantly more males in the cohort (77.3%) and most presented with macroscopic hematuria (71%). The authors reported on delays based on symptoms. The only symptom in common with OAB was "urgency," where 49 patients (14.3%) presented with that complaint alone, leading to a median of 45 days of patient delay in

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

seeking consultation, and 114 days of physician delay in seeking diagnosis. The median patient delay following any initial symptoms was 15 days (mean 141 days). The median doctor's delay, overall, was 62 days. The authors note that complaints of urinary urgency were more common with advanced cancers ($p < 0.002$). Delays in diagnosis appear to be quite long in duration from the time a patient presents until they are referred to a subspecialist. It did not appear that there was worsening of stage progression correlated with diagnostic delay, nor were there significant changes in survival. Bladder cancers are generally slow-growing. The authors theorize that urgency is often misinterpreted as caused by infection, leading to prescription of antibiotics first.

Reviewer's comment: It does not appear that availability of oxybutynin in the OTC setting would significantly increase the risk of delay of bladder cancer diagnosis.

UTI

UTIs are very common, particularly in women. They can frequently present with urinary frequency and urgency, but usually occur in an acute setting as opposed to OAB where symptoms are chronic. They are more typically coincident with dysuria, pain or foul-smelling, cloudy urine. UTIs can be self-limited depending on the etiology, but if they progress to the upper tract, i.e., pyelonephritis, symptoms will also progress to fever, chills and flank pain. While untreated pyelonephritis can lead to long term renal damage, such symptoms will prompt consumers to seek professional medical evaluation and management. Also see **Table 23**. Typically, UTI-related urgency and increased frequency are due to bladder irritation and inflammation. Oxybutynin may reduce some of the OAB symptoms, but clearly will not treat the etiology, nor manage other symptoms such as dysuria, hematuria or associated pain.

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

Data from PADERs and PSURs identified few UTI-related events ($n=245$; 1.8%). Of these, there were 13 SAEs, but there was no information on whether use of oxybutynin led to delays in diagnosis of any cases. AERS and WHO data were similar. Proposed labeling for Oxytrol for Women® warns consumers not to use the drug if typical UTI symptoms, i.e., dysuria, hematuria, cloudy urine, foul-smelling urine, or back or side pain are present. Such symptoms have a high likelihood of association with UTI. The label also specifically warns about UTIs and instructs consumers that symptoms of OAB should be present for at least three months before choosing to use oxybutynin. There does not appear to be any published or postmarketing clinical trial data indicating that use of Oxytrol® delays diagnosis of UTI.

Pregnancy

Urinary frequency and urgency are common in pregnancy. Proposed label instructions and warnings about possible early pregnancy should be adequate to ensure that women who have OAB symptoms, but who may be pregnant, take measures to confirm the diagnosis. Proposed use is for women who have had at least three months of OAB symptoms, likely minimizing any risk of delaying pregnancy diagnosis. Additionally, the label includes a warning to speak to a health professional if pregnant or breastfeeding due to the Category B designation. Even if women with an early pregnancy choose to use the drug, the obvious progression of pregnancy will likely result in stopping use and seeking prenatal care. One report in the literature indicates that over 50% of women in that study cohort had OAB symptoms in their first trimester¹⁴, thus supporting the proposed label warnings.

This reviewer performed an AERS search of “oxybutynin” within the Pregnancy and Neonatal Topics SMQ which includes several PTs related to pregnancy and congenital anomalies. I identified 39 cases. There were a few reported cases of early spontaneous abortion, one early neonatal death and anomalies such as cleft lip and palate. Some of these events are not infrequent regardless the drug exposure, and the cases often reported concomitant medications and other medical diagnoses that could contribute to the anomalies or events.

Skin Reactions

Use of the Rx Oxytrol® product is often associated with local dermal reactions. Such reactions account for the most frequently reported AEs in clinical trials and postmarketing experience. Since 2004, worldwide, spontaneous, postmarketing reports include over 4700 cases of skin-related disorders, with nearly 9700 AEs. Application site erythema and pruritis account for over 25% of all AEs. Most reactions are mild and resolve spontaneously once the patch is removed. Several warnings are proposed in the Drug Facts label, and the directions to rotate patch site placement and limit use to four days seem appropriate. True allergic skin reactions have been reported rarely.

Anticholinergic-specific Events

Data described elsewhere support the significantly lesser reporting of anticholinergic events for transdermal oxybutynin compared to that with use of oral forms. Dry mouth is still the most frequently reported anticholinergic-related event with transdermal use. Data from spontaneous reporting is described further above, however, of all anticholinergic-related events, very few were SAEs. The applicant proposes to include only warnings in labeling for OTC use that would be “useful” to the OTC consumer to support safe use. Therefore, they propose including only those events that may impact safety, i.e., sleepiness, dizziness, and blurred vision. Other warnings, such as for dry

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

mouth or constipation, are not proposed due to the purported low likelihood of occurrence.

*Reviewer's comments: See **Section 9.2 Labeling Recommendations** for further comments on inclusion of additional anticholinergic-related effects.*

Acute Urinary Retention

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

Narrow Angle Glaucoma

The applicant addressed whether consumers may be at risk of acute angle closure when using oxybutynin if they have narrow angle glaucoma. Some OTC drugs with anticholinergic properties, such as antihistamines, have simple label warnings that appear adequate for safe use in the OTC setting, i.e., postmarketing experience has not identified a safety concern. The published literature for oxybutynin includes a single report of an 80 year-old woman with acute angle closure brought on by oxybutynin use¹⁵ in the Rx setting. Oxybutynin's postmarketing experience also does not identify a safety signal. Proposed labeling warns specifically against use if consumers have narrow angle glaucoma.

Falls, Confusion and Disorientation

While anticholinergic effects, i.e., sleepiness, dizziness, and blurred vision, may contribute to increased risk of falls, it is important to note that falls and injuries may be a separate risk of OAB symptoms, particularly in older patients who have urinary urgency¹⁶. Older persons are also more likely to have age-related cognitive

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

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

impairment, co-morbidities and use concomitant medications that may increase their risk for various nervous system and psychiatric disorders. See **Section 7.5.4 Drug-Disease Interactions**.

This reviewer has commented on falls, confusion and disorientation in the context of anticholinergic-related effects. See the section **PSUR/PADER Review** above for further discussion of falls and injuries. See also the section **Tracked Safety Issues** above for details on cases of so-called “disorders of consciousness.” The applicant did not identify any reports in the literature describing falls or injuries due to CNS-related events following use of transdermal forms of oxybutynin. There does not appear to be any signal for clinically relevant changes in memory, cognition or mental status with use of oxybutynin. There were a few reports in postmarketing databases, but none that indicate a new safety signal.

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

Wagg et. al.¹⁷ reviewed the data on cognitive effects of antimuscarinic drug use, including oxybutynin, in elderly patients with OAB. They note that older persons are sometimes less likely to be prescribed drugs for OAB due to concerns about safety, tolerability and side effects in light of age-related cognitive deficits or early-stage dementia. Potential drug interactions or drug potentiation are also a concern as older persons may be on several drugs with anticholinergic properties. Also, patients with conditions such as Parkinson’s disease and cerebrovascular ailments may be more susceptible to the drug’s effects. In addition, the composition of oxybutynin compared to other anticholinergics for OAB (smaller molecular size, high binding affinity for M₁ receptors, high lipophilicity) make it more likely to cross the blood-brain barrier, where effects on the brain, and cognition, may be greater. Wagg summarized available data on cognitive impairment as it relates to several OAB drugs, including oral oxybutynin. Authors of one reference evaluated significant cognitive effects comparing use of oxybutynin to diphenhydramine and placebo in a randomized, double-blinded controlled trial of 12 subjects¹⁸. In nearly 50% of cognitive tasks, oxybutynin users had decreased performance when compared to diphenhydramine. Wagg et al. recommended that older users of drugs with anticholinergic properties consider the risk for initiation or worsening of existing cognitive impairment.

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

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

*Reviewer's comments: Based on review of the full complement of postmarketing safety data, this reviewer believes that the data do not suggest that there are any safety signals which would preclude approval for OTC marketing. It seems that any precautions or potential risks associated with use of Oxytrol for Women® can be properly labeled (see **Section 9.2 Labeling Recommendations**). Whether consumers respond to such warnings appropriately, guiding proper use of the product, is addressed in my review of the CONTROL trial elsewhere.*

9 Appendices

9.1 Literature Review/References

A literature search was conducted for review of pertinent articles published between 1996 and August 31, 2011. The search included key words “oxybutynin,” “Oxytrol,” “Gelnique,” or “Ditropan.” The focus of the search was on safety related to special populations, risks of overdose, and associations with use of concomitant medications or comorbidities. The applicant identified 31 pertinent articles from an initial list of 220. Only one reference had not been submitted to support the original Rx approval. This was a summary of the MATRIX study¹⁹. All other literature, contributing potentially useful safety information, described use of oral oxybutynin. Many references are single case reports often reporting use in the elderly.

Some references include infrequent or rare neuropsychiatric events. Interestingly, one of these reports was of a user with a history of mental illness abusing oxybutynin for some of its neuropsychiatric anticholinergic effects²⁰. Both auditory and visual hallucinations have been reported with use of both oral and transdermal forms of oxybutynin. In a review of AERS data, within the Psychiatric Disorders SOC, there were 27 events reported that indicate mood changes, hallucinations, drug dependence or similar events. There were significantly more events reported with use of oral forms. No new safety signals were identified.

Reviewer's comments: Overall, the bulk of the oxybutynin literature references oral forms with evaluation of AEs that are relatively more frequently reported compared to patients who use transdermal forms. Many reports evaluated rare, but interesting events. Labeling for potential interactions with CYP3A4 inhibitors are addressed below. The applicant submitted additional references at the 120-day update, July 27, 2012. None of these references included data on transdermal forms of oxybutynin. This reviewer assessed the safety reported in a few pertinent papers describing original trials of transdermal use in women:

¹⁹ Newman DK, 2008, The MATRIX Study: Assessment of Health-related Quality of Life in Adults with the Use of Transdermal Oxybutynin, *Director*, 16: 15-19.

²⁰ Guloksuz S, 2010, A Case of Oxybutynin Dependency, *Gen Hosp Psychiatry*, 32: e5-e6.

- **Davila 2001¹¹**: *The authors assessed efficacy, safety and tolerability of transdermal use versus oral forms of oxybutynin in 76 symptomatic patients. Most patients were female and over 60 years of age. Dose titration was based on tolerability of anticholinergic side effects. Up to four patches (three patches = oxybutynin 3.9mg/day) could be applied twice weekly. The study duration was six weeks. Though it was the most frequent event reported, significantly fewer patients had dry mouth with transdermal use, and most (90%) had none or mild skin erythema.*
- **Kennelly 2009**: *This report evaluated subjects with neurogenic bladder who received escalating doses of transdermal oxybutynin plus clean intermittent catheterization. Up to 3x the usual daily dose (3.9 mg/day) was administered to male and female subjects who met the enrollment criteria. The trial duration was eight weeks. Only 12% of subjects (n=24) were female, and the average age was 42 years. Three subjects reported application site reactions; two reported dry mouth. AE reporting rates appeared to be independent of dose strength. No subjects discontinued due to AEs.*
- **Sand 2011**: *This is an analysis of a 12-week, phase 3 trial for efficacy and safety of Gelnique® use in female OAB patients. Subjects who received test drug (n=352) had a mean age of 59 years. Less than 5% of discontinuations were due to AEs, and the difference between AE reporting in the treatment and placebo groups were insignificant. Reports of dry mouth were more frequent in the treatment group, and significantly greater than in the placebo group. Application site reactions were not commonly reported.*

References

Kennelly MJ, GE Lemack, JE Foote, CS Trop, 2009, Efficacy and Safety of Oxybutynin Transdermal System in Spinal Cord Injury Patients with Neurogenic Detrusor Overactivity and Incontinence: An Open-label, Dose-titration Study, *Urology*, 74: 741-745.

Sand PK, GW Davila, VR Lucente, H Thomas, KE Caramelli, et. al., 2011, Efficacy and Safety of Oxybutynin Chloride Topical Gel for Women with Overactive Bladder Syndrome, *Am J Obstet Gynecol*, 206: 168.e1-6.

9.2 Labeling Recommendations

The following are proposed as additional considerations to be addressed during labeling negotiations with the applicant (see **Figure 5** for the proposed label):

Use and Directions

- The drug's use should be revised to state "relieves symptoms of overactive bladder in women." The term "treats" implies that oxybutynin is effective for all causes of OAB symptoms. Consumers should not have the impression that this drug can replace appropriate medical diagnosis and treatment of secondary causes of OAB symptoms.

- The “Use” section may include a statement about “first-line treatments”²¹ including behavioral therapies as alternatives to or in combination with pharmacologic therapy such as Oxytrol for Women®.
- On August 27, 2012, the applicant submitted data in response to a request to provide quality-related reports or complaints from the CONTROL trial. See **Section 4.1 Chemistry Manufacturing and Controls** for further details. Several subjects reported patches falling off within the labeled four days of use per patch. In the directions for use, the applicant should include a statement to address what to do if a patch falls off. Oxytrol® prescription labeling tells consumer to put on a new patch in a different area if the patch falls off and can’t be pressed back into place.

Safety

- The proposed label warns consumers to ask their doctor or pharmacist before use if taking another prescription medication for OAB. Instead, consumers should be warned to cautiously use any additional drugs that may have anticholinergic side effects or may be associated with side effects such as dry mouth, constipation, or somnolence. Risk for such effects may be compounded.
- The label should consider the potential risks of oxybutynin use and effects on cognition, particularly in older consumers who may have underlying impairment or dementia, CNS-related co-morbidities, or who are using concomitant phosphodiesterase inhibitors (see the first safety concern in Section **Tracked Safety Issues** above) or other drugs with anticholinergic properties²². See **Section 7.5.4 Drug-Disease Interactions**.

Reviewer’s comments: This reviewer proposes three warnings:

- *ask a doctor before use if you are taking other anticholinergic drugs or cholinesterase inhibitors. Such a precaution with concomitant use of anticholinergics is present in labeling for cholinesterase inhibitors.*
 - *Consumers over age 65 should ask a doctor before use.*
 - *stop use and ask a doctor if you have worsening memory, confusion or agitation while taking the product.*
- No specific drug-drug interactions have been tested. Because oxybutynin is primarily metabolized by the CYP3A4 system, concomitant use of moderate or strong inhibitors of the system should be used at the discretion of the consumer’s doctor or pharmacist.

21 Gormley EA, DJ Lightner, KL Burgio, TC Chai, JQ Clemens, DJ Culkin, et. al. (Overactive Bladder Panel), 2012, Diagnosis and Treatment of Overactive Bladder (Non-neurogenic) in Adults: AUA/SUFU Guideline, American Urological Association (AUA) Guideline, American Urological Association Education and Research, Inc. p. 1-36.

22 Staskin DR, 2005, Overactive Bladder in the Elderly – A Guide to Pharmacological Management, *Drugs Aging*, 22: 1013-1028.

Reviewer's comments: This reviewer found one article²³ reporting testing of interactions between oral oxybutynin and a potent CYP3A4 inhibitor, itraconazole. Ten healthy subjects participated in a randomized, double-blind, two-phase, cross-over design trial with 200 mg itraconazole or placebo, and 5 mg oxybutynin. Dosing occurred once daily over a four day treatment period. While the oxybutynin concentration was two-fold larger ($p=0.0007$) during the itraconazole exposure phase, the AUC of NDEO ($p=0.57$) was not affected to great degree. Elimination half-life did not change. Oral bioavailability of oxybutynin averages only 6%, so the increased concentration with concomitant itraconazole exposure may be minimally clinically significant. Metabolism of oral oxybutynin occurs rapidly, resulting in an increase in NDEO concentration with persistence of the drug effect. Transdermal application bypasses first pass metabolism in the gut and liver, limiting risk for side effects, but, that risk, or risk of overdose, may still be higher when Oxytrol for Women® is used concomitantly with strong CYP3A4 inhibitors.

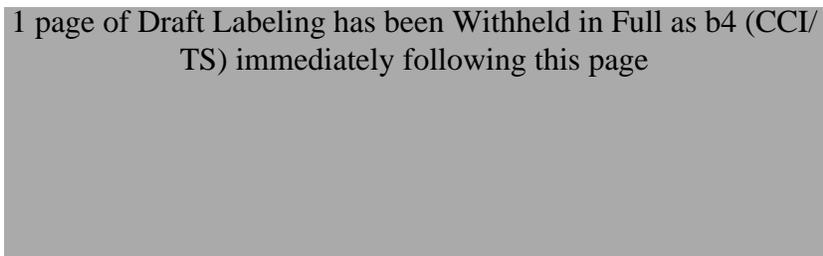
- The label should instruct subjects with diagnoses of ulcerative colitis, myasthenia gravis and gastroesophageal reflux disease or esophagitis to speak with their doctor before using Oxytrol for Women®. These conditions may be affected by anticholinergic-related decreased gastrointestinal motility. The diagnoses should be described in consumer-friendly terms that are well-understood.
- We should consider adding a statement such as “your symptoms may be due to a more serious condition” to the bullet instructing men not to use the drug.
- Foreign labeling includes warnings that symptoms of hyperthyroidism, coronary heart disease, congestive heart failure, arrhythmias, tachycardia, and hypertension may be worsened. Consider a warning to ask a Doctor before use if consumers have cardiac disease.
- The label should include “dry mouth” and “constipation” under the “When using this product” section. These are bothersome anticholinergic-related effects reported by users of the prescription drug. Constipation is considered as part of the Beers criteria (see **Section 7.5.4**).
- The OTC label should instruct consumers not to drive or operate heavy machinery until they know how Oxytrol for Women® will affect them. This language was added as class labeling to the prescription labeling in October 2012 following review of postmarketing information.

23 Lukkari E, A Juhakoski, K Aranko, PJ Neuvonen, 1997, Itraconazole Moderately Increases Serum Concentrations of Oxybutynin but Does Not Affect Those of the Active Metabolite, *Eur J Clin Pharmacol*, 52: 403-406.

Clinical Review
Ryan Raffaelli, M.D.
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Oxytrol for Women® (Oxybutynin Transdermal System 3.9 mg/day)

Reviewer's comments: This reviewer proposes a warning such as "When using this product, sleepiness, dizziness, or blurred vision may occur. Do not drive or operate heavy machinery until you know how Oxytrol for Women® affects you."

1 page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



9.3 Advisory Committee Meeting

The product is a new class of drug to be introduced to the OTC consumer. The applicant proposes an indication for Oxytrol for Women® that is novel to the OTC marketplace. Approval relies on postmarketing safety data, and the results of several consumer behavior studies to support safe and proper use. FDA presented data and results of our analyses to the Nonprescription Drug Advisory Committee, including urologic and women's health specialists, to seek advice as to whether the proposed drug is appropriate for OTC marketing. The meeting was held on November 9, 2012.

The committee had several concerns that should be considered:

- Nearly 80% of subjects who wished to purchase the drug reported any label ineligibilities. The committee felt that it was clear that consumers are either unlikely to read the Drug Facts label, or may disregard warnings and precautions. Some members were concerned that consumers may be unable to appropriately self-diagnose and self-select, and that many users did not stop use after experiencing new or worsening symptoms. They considered whether the label should convey that consumers have a diagnosis of OAB prior to purchase and use, stressing the importance of physician involvement and urinalysis to exclude more serious conditions.
- While consumers may not properly select to use the drug, and some post-hoc misuse rates addressing major endpoints were high, the committee acknowledged that the safety data from the CONTROL trial and postmarketing experience supported the application.
- The committee expressed concern about use of the drug by older consumers (> 65 years) citing the known CNS-related anticholinergic effects of oxybutynin and the Beers criteria for potentially inappropriate medications.
- The committee supported inclusion of a consumer information leaflet as part of labeling. The leaflet may more fully inform consumers about OAB as a diagnosis of exclusion, and include, for example, information on non-pharmacologic behavior therapies as well as risks associated with use of anticholinergic drugs.
- The committee expressed concern about off-label use by men and children with enuresis.

Ultimately, the committee voted 6-5 that the data in the application did not support that consumers can appropriately self-select to use oxybutynin transdermal system in an OTC setting. However, two members on the "Nay" side commented that they would be supportive of approval if a consumer leaflet were included as described above, and if consumers over age 65 were warned to seek the advice of their doctors before use. The latter label revision would also limit risk of delayed diagnosis of bladder cancer since older consumers are more likely to contract the disease.

Reviewer's comments: This reviewer has addressed most of the concerns in the review and in my labeling recommendations. I will address some points here. I do not agree that the label include a statement that consumers have a diagnosis of OAB prior to purchase and use. It does not appear necessary. Most subjects in the CONTROL trial who wished to purchase the drug met the OAB symptom conditions, and the Advisory Committee did not question these proposed conditions. Many subjects reported having a prior diagnosis of OAB as well, and consumers can easily identify OAB symptoms. Available data also support that symptoms of more serious conditions are either easily recognized, or that diagnosis of such conditions are not delayed unnecessarily by use of the drug. FDA originally discussed inclusion of a urine dipstick and testing strips with the applicant. The applicant believed that a dipstick would introduce a level of complexity too great to support proper use in the OTC setting. That may be true. The use and safety data from the CONTROL trial indicate that consumers can distinguish OAB symptoms from those of acute UTI.

Available data indicates that diagnosis of diabetes and bladder cancer may be delayed in the "real world," and the data do not indicate that short term use of Oxytrol for Women® in the OTC setting would lead to further, clinically relevant delays. In fact, OAB symptoms due to these conditions are unlikely to improve with use of oxybutynin. Consumers will simply stop use and may be more likely to seek medical advice if their OAB symptoms do not improve. Data from the CONTROL trial supports this. Many subjects in the trial, and OAB sufferers in general, appear to attempt to self-manage their symptoms for months if not years prior to seeking therapy. OTC availability of the drug may simply open access to one option for management.

A consumer information leaflet will require discussion between FDA and the applicant. Several points could be made in an available leaflet, similar to the patient information provided with the Rx product, but a specific proposal should be made by the applicant. Language in the leaflet should be well understood by the consumer.

There are data in the consumer behavior program addressing potential off label use. Very few men sought to participate in the CONTROL trial (1.8% of those screened). Although prior self-selection study of men indicated that more than 10% were interested in using the drug, the applicant's proposed pink packaging, tradename, female image on the package, and label should help deter men from using the drug. Also see the labeling recommendations. Regarding use by children with enuresis, subjects in the initial label comprehension study appeared to well understand instructions that children under age 18 should not use the drug.

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/s/

RYAN M RAFFAELLI
11/18/2012

LESLEYANNE FURLONG
11/19/2012

CLINICAL FILING CHECKLIST FOR NDA 202211

	Content Parameter	Yes	No	NA	Comment
	well-controlled studies in the application?				efficacy data from original NDA. A single AUS submitted.
15.	Do all pivotal studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements?	x			Sponsor did not include proportion of subjects who did not improve after 2 weeks as primary endpoint, but as a secondary. They stated this at 9/11 meeting without a response from FDA.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			Rationale provided for excluding non-transdermal data. ISS section 3.3.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			DRUP believes an adequate number of patients were exposed (At any strength, over 300 for 6 months; 74 for one year) for Rx approval of the NDA. Safety of oxybutynin is well known; max daily dose is low; dermal irritation studies support safe use.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA 202211

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Special safety topics have been addressed (falls, disorientation, confusion, anticholinergic effects)
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?	x			
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Product does not appear to trigger PREA.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal consumer behavior studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			Defer to stats
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	x			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 202211

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Application is fileable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Please provide several literature references for our review (Module 2.7.5): References 3, 26, 76, 122-136, 174, and 216.
- For the following subjects with mitigation profiles created (Subject IDs: CL2008-13-10-0133, CL2008-13-12-0086, CL2008-13-11-0019, CL2008-13-17-0124, CL2008-13-26-0152, CL2008-13-30-0084, CL2008-13-16-0019, CL2008-13-32-0058), please provide a link to their Case Report Form (CRF) so that we can more fully evaluate the mitigation assessment.
- Table 14-14-45 lists those subjects who were considered misusers, based on the Secondary Endpoint 3, and who were assessed for mitigation. Please provide the CRFs for the following subjects (Subject number: CL2008-13-10-0021, CL2008-13-10-0025, CL2008-13-11-0098, CL2008-13-19-0007, CL2008-13-25-0028, CL2008-13-23-0067) so that we can more fully evaluate the mitigation assessment.
- Section 11.1.7 of the final study report for Protocol CL2008-13 describes patch misuse based on Secondary Endpoint 5. Misuse was assessed for mitigation. If a table similar to Table 14-14-45 (“Secondary Endpoint 3: Listing of Misusers and Mitigation Assessment with Reasons for Mitigation by Subject Number”) exists for Secondary Endpoint 5, please identify its location. If no such table exists, please provide a similar table for subjects who misused the drug by multiple simultaneous patch use.

Ryan Raffaelli	May 2, 2012
Reviewing Medical Officer	Date

Lesley Furlong	May 2, 2012
Clinical Team Leader	Date

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

/s/

RYAN M RAFFAELLI
05/02/2012

LESLEYANNE FURLONG
05/02/2012