NONPRESCRIPTION OXYBUTYNIN TRANSDERMAL PATCH: IMPROVING SELF CARE OPTIONS FOR OVERACTIVE BLADDER IN WOMEN

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On January 25, 2013 the US Food and Drug Administration (FDA) announced the approval of the Rx-to-OTC switch of oxybutynin in the form of Oxytrol® Transdermal System (TDS) for women suffering from overactive bladder (OAB). This represents a first-in-class switch for a chronic condition. The FDA’s decision to approve Oxytrol® For Women is an important advance in patient self-care. This represents the culmination of an interactive review of the sponsor’s New Drug Application (NDA) and the FDA’s considerations of the deliberations of a public FDA Advisory Committee meeting on November 9, 2012. Oxytrol® Transdermal System remains a prescription product in other countries where it is marketed.

Key words: Nonprescription, transdermal patch, overactive bladder women, oxybutynin.

OVERACTIVE BLADDER: PREVALENCE AND IMPACT ON QUALITY OF LIFE

Overactive Bladder (OAB) is one of the most common chronic conditions among women, with an estimated 17% of adult women in the United States, or just over 20 million, suffering from symptoms. OAB is clinically defined by urinary urgency, with or without urge incontinence, and is usually associated with urinary frequency and nocturia. OAB may occur in women of any age, although it is typically associated with aging and increasing prevalence between the ages of 45 and 60. While OAB is not life-threatening, it is lifestyle-limiting and has a well-documented impact on health-related and overall quality of life (QoL) measures.

While women are readily able to recognize the symptoms of OAB, most choose to manage the condition on their own, often employing a variety of lifestyle modifications (e.g., bladder training, pelvic floor exercises), coping mechanisms (e.g., restricting intake of fluids, bathroom mapping), and reliance on absorbent products rather than visit a doctor and receive a prescription. Furthermore, consumer research to support this development program found that one-third of women with OAB have never discussed their condition with their physician.

PHARMACOLOGIC AND CLINICAL FEATURES OF THE OXYTROL® PATCH

While there is no cure for OAB, the oxybutynin transdermal system (Oxytrol TDS) provides meaningful symptom relief for many people with OAB. The active ingredient, oxybutynin
has been available by prescription in oral forms for over 30 years. It blocks the action of acetylcholine at receptors in bladder smooth muscle. Oxytrol TDS was approved by the FDA in 2003 and has had approximately 270,000 patient-years of marketed use since product launch through the period ending February 25, 2011. It is especially well-suited for OTC availability based on its efficacy and safety profile. It delivers oxybutynin continuously and consistently over a 3 to 4 day period directly into systemic circulation, avoiding first-pass gastric and hepatic metabolism which converts oral oxybutynin to an active metabolite N-desethyloxybutyin (N-DEO) which is associated with much of the anticholinergic side effect profile associated with oral products. N-DEO levels are markedly lower with transdermal delivery, helping to improve tolerability. The once every four day regimen and sustained lower plasma levels promote better adherence and avoid the peaks and troughs of active moieties with oral treatment.

In pivotal studies supporting regulatory approval of the prescription product, oxybutynin TDS was associated with statistically and clinically significant reductions of OAB symptoms compared to placebo, including incontinence episodes, urinary frequency, and mean void volume. Anticholinergic side effects were slightly more frequent than with placebo but substantially less than seen with oral oxybutynin and tolterodine suggesting better tolerability than either of these orally administered drugs. Like other OTC transdermal patch products, there is some degree of skin irritation observed with the use of oxybutynin TDS. Thus, oxybutynin TDS has efficacy comparable to oral oxybutynin products with an improved anticholinergic side effect profile. Clinical studies have also measured a range of Quality of Life improvements, similar to other products in this class. The oxybutynin TDS product (3.9 mg/day) approved by FDA for OTC use is the same dose and formulation as that approved for prescription use to treat the symptoms of OAB.

**OXYTROL OTC DEVELOPMENT PROGRAM: SELF-MANAGEMENT LABELING SAFEGUARDS**

The main rationale for a product to be considered appropriate for use without direct involvement of a healthcare professional employs four basic approaches (Figure 1) to risk reduction.

*Figure 1: Self-Management Labeling Safeguards*
• The product must have well-established efficacy and a safety profile appropriate for nonprescription use.

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

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

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

With these tenets in mind, the Oxytrol OTC development plan took the following approaches to labeling:

• The target population was limited to adult women. Men who have symptoms of OAB may require a prostate exam and should not use nonprescription Oxytrol without a professional recommendation.

• A prominent warning was added to the label to alert consumers that other conditions may also have urinary symptoms similar to those of OAB. These other conditions, although usually presenting with an array of symptoms, may also include urinary frequency and urgency (e.g., pregnancy, UTI, diabetes, or even bladder cancer). In such cases there may be a risk that use of OTC Oxytrol might delay professional diagnosis and/or treatment of the non-OAB condition.

• The label also instructed that OAB symptoms should be present for at least 3 months to reduce the risk that women do not use the product if they have more acute symptoms that may be associated with UTI or early pregnancy.

• The OTC label also included a directive to seek medical care if no improvement is seen within a conservative 2-week time period, the earliest that most women would feel a meaningful effect, although some will start to feel the effect earlier.

Thus, the OTC label helps women identify potential underlying disorders that could also present with urinary symptoms. This alone provides an important benefit not being offered by the absorbent products used by women to self-manage their OAB.

Initial Label Comprehension testing aimed at measuring how well the label was understood by general and targeted populations. Self-selection studies assessed the decisions of targeted consumers on whether or not the product was appropriate for their use, considering their medical history and personal status (see Figure 2).
Figure 2: Oxytrol Switch Development Program Studies

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INITIAL LABEL COMPREHENSION STUDY RESULTS

- Respondents demonstrated excellent comprehension of the product’s use for treatment of OAB (96-100%) and showed strong understanding of OAB symptoms (83-91%).

- Recognition that symptoms of possible urinary tract infections or other more serious conditions preclude use also achieved high scores: blood in the urine (94%), lower back pain (91-95%), and pain when urinating (91-92%) were consistently understood. Males understood the message that the product is not for men (95%).

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

INITIAL SELF-SELECTION STUDY RESULTS

- All subjects had OAB symptoms and included normal literate (NL) and low literate (LL) cohorts of women as measured by the Rapid Estimate of Adult Literacy in Medicine test, REALM Test, as well as a third mixed cohort of adults with at least one of four key conditions: being male, having diabetes, having glaucoma, or being pregnant or breast-feeding. Responses from subjects on whether or not the product was appropriate for them to use after reading the label were compared to those of physicians who also read the label and conducted an examination of the subjects, including urinalysis and pelvic examination.

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

- 92% or more respondents in the NL and LL cohort made a self-selection decision which was consistent with a physician or which was associated with minimal or no risk.
TARGETED SELF-SELECTION AND LABEL COMPREHENSION STUDY RESULTS\textsuperscript{14}

- 90% of men self-selected appropriately.
- 93% of women of childbearing age understood the enhanced pregnancy warning.
- 92% of pregnant women self-selected appropriately.
- For label messages about diabetes, a general population of women with OAB symptoms attained scores of 93-94% and respondents with some risk for diabetes scored 88-89%.
- Women aged 65 years and older understood the directions for use and important safety warnings with nearly all important messages achieving 80% or higher understanding.

PIVOTAL LABEL COMPREHENSION STUDY RESULTS IN WOMEN WITH OAB\textsuperscript{14}

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

The results from this series of label comprehension and self-selection studies supported a conclusion that the label messages on directions for use and the key safety warnings are well understood by the broad target population as well as important cohorts (such as men, pregnant women, low literate individuals). Thus, the label should effectively guide self-selection, providing the second layer of the Self-Management Labeling Safeguards depicted in Figure 1.

ACTUAL USE STUDY – CONTROL\textsuperscript{14}

The modified label which was studied in the second stage of consumer research was also used in the Actual Use Study, CONTROL (CONsumer TRial of OxytroL). The objective of CONTROL was to evaluate ongoing use behavior in potential consumers. Although, the Label Comprehension and Self-Selection studies were deemed successful, they also revealed that a small percentage of consumers might still misunderstand or disregard label instructions. Thus, the CONTROL study was designed without a rigorous self-selection component and with minimal exclusions in order to allow observations of use by consumers who did not meet all label criteria and might purchase the product. This enabled assessment of use behavior and potential safety risks in consumers who may stray from certain label directions in the actual marketplace. All elements of each subject’s observed behavior, including open-ended interview responses were applied to the determination of correct or incorrect decisions. The primary endpoint was the error rate for stopping use if new symptoms defined in the label (abdominal and pelvic pain was added at the request of the FDA but this symptoms were not indicated in the label) occurred or if OAB symptoms worsened at two weeks. Pre-specified criteria for a successful study defined an upper confidence interval (CI) of $\leq 5.0\%$. 
A call center screened 2,731 potential subjects and 1,230 visited one of the sites for an enrollment interview, of which 727 provided verified Oxytrol use data for up to 12 weeks to treat OAB symptoms.

The primary endpoint was met. Of the 727 subjects, 3.4% of verified users failed to stop using Oxytrol when they should have (95% CI: 2.2%, 5.0%). The point estimate is determined through a data adjudication process called mitigation and is subject to medical interpretation in some cases\(^\text{16}\). The findings were consistent by age, race, and literacy.

Additional secondary endpoints examining consumer behavior also demonstrated appropriate ongoing use decisions, although some women reported that they needed longer than two weeks to assess whether or not the product was working for them.

98% of women (60/61) who developed a UTI during the study acted appropriately.

The safety experience was consistent with the approved prescription product labeling and no new adverse events of concern emerged in this 12-week Actual Use Study. Patch irritation was the most commonly reported adverse event.

Thus, even with participation of women using the product who did not meet all label criteria, the CONTROL study demonstrated that the vast majority of inappropriate users would stop using the product within the first two weeks. This fulfills the third layer of the Self-Management Labeling Safeguards depicted in Figure 1.

**BENEFIT AND RISK CONSIDERATIONS FOR NONPRESCRIPTION ACCESS TO OXYTROL**

OAB is currently a condition that most women choose to self-manage. It is associated with a decreased QoL, an increased risk of depression, and reduced work productivity. Many sufferers do not seek physician treatment even when QoL is significantly impacted because they believe that OAB symptoms are an unavoidable consequence of aging and do not realize that OAB is a treatable medical condition\(^\text{17}\). Due to the negative social stigma, shame and embarrassment commonly associated with this condition, many women wait years after initial onset of OAB symptoms before deciding to discuss their symptoms with a healthcare provider\(^\text{17}\). They choose instead to adapt their lives with a myriad of self-management strategies that can create substantial self-imposed restrictions on their lives.

Nonprescription Oxytrol® will provide a convenient treatment option for women currently managing OAB with absorbent products and other restrictive self-management strategies. Although the effect size seen in placebo controlled studies is moderate, for those women who respond, Oxytrol does produce symptom and QoL improvements. Additionally, we believe nonprescription labeling, and accompanying education and support programs, will also increase awareness that urinary frequency can possibly be a symptom of other undiagnosed conditions such as UTI and diabetes. Ideally, this could even lead to earlier diagnosis of other conditions and overall public health may be improved as women gain more understanding and control of genitourinary health.
The availability of Oxytrol as an OTC product should not present any greater risk than already being incurred by women who self-manage OAB. In fact, it may actually have the potential to reduce consumer risk via responsible consumer education compared with the use of absorbent products and other OAB self-management strategies. The theoretical risks from making Oxytrol available OTC include a potential delay in diagnosis of UTI, diabetes, bladder cancer, and pregnancy. However, while urinary frequency and/or urgency can be present in all of these conditions, there are other more obvious clinical characteristics of these underlying diseases and conditions which are separate and distinct from OAB. Thus, it was concluded that Oxytrol for Women could be used safely in an OTC setting, even if some users made mistakes or did not meet all labeled eligibility criteria.

Although OAB may be viewed as one of the first chronic conditions for which FDA has approved an Rx-to-OTC switch, the OTC treatment of OAB symptoms is largely consistent with other OTC switch paradigms. Conditions like allergy and frequent heartburn are chronic but intermittent and of varying intensity and individual perceptions. OTC medicines help reduce symptoms and allow people to experience an improved quality of life and participate in regular daily lifestyle activities.

EFFECTIVE LABELING REDUCES POTENTIAL RISKS TO ACCEPTABLE LEVELS

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

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

Taken together, the results of the label comprehension and self-selection studies predict that the Oxytrol Drug Facts label will be about 80% to 95% effective in communicating key messages regarding self-recognition of OAB and product use. Once a woman decides to use the product, the CONTROL study predicts that the label is 80% to 95% effective in driving appropriate ongoing use decisions about when to stop or continue use. This includes meeting the pre-defined primary endpoint of CONTROL for which greater than 95% of users made appropriate de-selection decisions. Following the self-management labeling safeguards depicted in Figure 1, it is predicted that, among the low percentage of consumers who might self-select incorrectly, the vast majority will appropriately discontinue use within a reasonable time of starting treatment.

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

CONCLUSION

Nonprescription access to Oxytrol® for Women will provide a favorable benefit with minimal risk to public health by:

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

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REFERENCES


13. Food and Drug Administration. FDA overview by Dr. Donald McNellis of the efficacy and safety database for NDA 21-351: Oxytrol (Oxybutynin Transdermal System [TDS]). Available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/NonprescriptionDrugsAdvisoryCommittee/ucm293603.htm


