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RESEARCH**

APPLICATION NUMBER:

202211s000

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: January 24, 2013
FROM: Julie Beitz, MD
SUBJECT: Approval Action
TO: NDA 202211 Oxytrol for Women (oxybutynin) transdermal system, 3.9 mg/day
MSD Consumer Care, Inc.

Summary

Oxybutynin is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Oxytrol is the tradename for an oxybutynin transdermal system that was approved as a prescription product under Watson Laboratories, Inc.'s NDA 021351 on February 7, 2003. Each transdermal system delivers 3.9 mg/day; a new system is applied twice weekly (every 3-4 days). The applicant of this NDA, MSD Consumer Care, Inc., has requested a partial prescription-to-over-the-counter (Rx-to-OTC) switch for Oxytrol for the treatment of overactive bladder in women only; the proposed tradename for the OTC product is Oxytrol for Women. There are no currently FDA-approved OTC treatments for overactive bladder.

The Divisions of Reproductive and Urologic Products (DRUP) and Nonprescription Clinical Evaluation (DNCE) have recommended approval for NDA 202211 for Oxytrol for Women (oxybutynin) transdermal system for the treatment of overactive bladder in women. This memo documents my concurrence with these recommendations. Discussions regarding the product labeling have been satisfactorily completed and there are no inspectional issues that preclude approval of the application.

Oxytrol will remain a prescription product for men given the potential that OTC availability of the product could either mask symptoms of, or delay treatment for, more serious conditions, such as bladder outlet obstruction or urinary retention, prostate or bladder cancer, or bladder carcinoma *in situ*. Thus, concurrent with the approval of this partial Rx-to-OTC switch, Watson Laboratories, Inc., the holder of NDA 021351 for the prescription Oxytrol product, [REDACTED] (b) (4)

Regulatory History

On April 16, 2007, a pre-IND meeting was held with Schering-Plough HealthCare Products to discuss the studies that would be conducted in support of a full Rx-to-OTC switch for Oxytrol. At the meeting, the Agency advised Schering that it would need "to define an appropriate target OTC population for use of the product given its risk-benefit profile", and "convincingly show" that this OTC population can distinguish symptoms of idiopathic overactive bladder from medical conditions that require the intervention of a learned intermediary. This advice was based on the fact that in clinical practice, the diagnosis of idiopathic overactive bladder is usually made after a complete history, physical examination (including a pelvic in women and rectal examination in men), and laboratory assessments, such as a PSA level, have ruled out other causes for the subject's urinary symptoms.

Also, at that meeting, the Agency advised that as Schering had rights of reference to the original Oxytrol NDA (021351), and [REDACTED] (b) (4) the prescription product, no new preclinical studies would be required to support the safety and efficacy of the product under OTC conditions of use.

On January 27, 2010, IND 074288 (received on January 28, 2010) was submitted by MSD Consumer Care Inc. following Merck's acquisition of Schering-Plough in 2009.

A pre-NDA meeting was held on September 12, 2011. MSD indicated that it would analyze the primary efficacy endpoint for the actual use study as stated in the protocol, i.e., as the proportion of users (that used at least one patch) who did not stop use when they developed either new or worsening symptoms in accordance with the label directions. MSD also agreed to amend the statistical analysis plan to include additional efficacy analyses that DNCE recommended. On March 26, 2012, MSD submitted NDA 202211 in support of a partial Rx-to-OTC switch for Oxytrol, for use by women only.

Advisory Committee Meeting. This application was discussed before the Nonprescription Drugs Advisory Committee on November 9, 2012. The Committee rendered a split vote (5 in favor, 6 against) regarding whether the available data support that consumers can appropriately self-select to use Oxytrol in the OTC setting. Those members who voted "No" were predominantly concerned about the anticholinergic adverse effects of the product, particularly among elderly users who may also be taking other medications with anticholinergic effects. Others maintained that 1) numerous products with anticholinergic adverse effects (such as antihistamines) are already widely marketed in the OTC setting, and 2) anticholinergic adverse effects are less common with use of the transdermal oxybutynin formulation as compared to oral formulations. Two of the members who voted "No" stated they would vote "Yes" if their concerns about safe use in the elderly were adequately addressed in product labeling.

Some members expressed concern that consumers could delay diagnosis and medical treatment of serious conditions such as diabetes, bladder cancer or bladder cancer *in situ*. Others maintained that before using this product, consumers should consider non-pharmacologic options, and consult with a pharmacist or physician. Panel members who voted "Yes" regarding self-selection stated that most consumers were already self-managing their symptoms of overactive bladder because of the perceived stigma, and the perception that their symptoms were a part of aging, and could not otherwise be helped. These members saw availability of this product in the OTC setting as an important treatment option that could also prompt further evaluation by a physician (in the event the product does not resolve the consumer's symptoms).

Product Quality Considerations

The currently marketed prescription Oxytrol product is a matrix-type transdermal system composed of three layers: a backing film that provides the system with occlusivity and physical integrity, an adhesive/drug layer of acrylic adhesive containing oxybutynin, and the release liner that is peeled off by the user and discarded prior to applying the system. The system is available as a 39 cm² system containing 36 mg of oxybutynin and has an *in vivo* delivery rate of 3.9 mg of oxybutynin per day through skin of average permeability. The Oxytrol for Women product will be identical to the currently marketed prescription Oxytrol product, except that the OTC product will have a child resistant layer added to the (b) (4) the pouch (b) (4).

Reports of difficulties removing prescription Oxytrol transdermal systems from their respective pouches prompted the staff of the Office of New Drug Quality Assessment (ONDQA) to consider the possibility that adhesive (b) (4) could extend beyond the backing film and be transferred to the pouch. On October 31, 2012, ONDQA requested that Watson Laboratories, Inc. submit a prior approval supplement (to NDA 021351) to establish test and acceptance criteria for (b) (4) to be used at release and on stability. In response to this request, Watson submitted a supplement dated December 21, 2012 which was received on December 26, 2012.

During the review of this application, MSD: 1) submitted a revised stability protocol to include tests for (b) (4) observation, and to revise the shelf-life to 24 months, and 2) agreed to change the text on the backing film to a darker ink within one year of approval. On January 17, 2013, Watson Laboratories, Inc. was requested to submit a prior approval supplement to NDA 021351 that would establish test and acceptance criteria for the absence of (b) (4) to be used at release and on stability of the prescription Oxytrol product, and that would revise the text font color on the backing film so that the prescription transdermal system would be more visible if it detached from the subject's skin.

Efficacy

In NDA 021351, the efficacy of Oxytrol was evaluated in subjects with urge urinary incontinence in two randomized, placebo-controlled trials of 12 weeks duration. In both trials, Oxytrol 3.9 mg/day significantly reduced the mean number of weekly (or daily) incontinence episodes and mean void volume at Week 12 compared to placebo treatment. In one of these trials, Oxytrol 3.9 mg/day also significantly improved the mean number of daily urinary frequency episodes at Week 12 compared to placebo treatment. There were no additional clinical efficacy trials submitted in support of the partial Rx-to-OTC switch application.

Safety

Several consumer studies were performed to support the partial Rx-to-OTC switch of Oxytrol. Multiple label comprehension studies and self-selection studies were performed in subjects of normal and low literacy to develop the label to be used in the pivotal actual use study.

Pivotal Actual Use Study. The results of the Consumer Trial of Oxytrol (CONTROL) were the primary results supporting the partial Rx-to-OTC switch for Oxytrol. The CONTROL study was a single-arm, multicenter study that included a 12-week use phase. Screening criteria required that subjects were female, over 18 years of age, not pregnant, and not trained or employed as a healthcare professional. At the pharmacy site, subjects were asked to view the package and make their own purchase decision. There was no self-selection component *per se*. Following a decision to purchase, a pharmacist performed a medical and demographic history.

Subjects who reported hematuria, or back pain and fever with overactive bladder symptoms and either dysuria, hematuria or cloudy urine, were excluded from entering the use phase and were referred to a physician for evaluation. Subjects kept a medication diary and were also interviewed at weeks 3, 7, and 12 (end of study).

Subject characteristics and disposition. In the CONTROL study, 1069 subjects decided to purchase Oxytrol; of these, 785 used at least one application of the product. The median age of subjects was 58 years (range 18-94 years), and a third were over 65 years. Thirteen percent were of low literacy. The median exposure to Oxytrol in the study was 45 days which is similar to the 1-2 month duration of use predicted by available drug utilization data for the prescription product.

Of the 1069 subjects who decided to purchase the product, 931 subjects (87%) had experienced two or more symptoms of overactive bladder for at least three months. However, 839 of these 1069 subjects (78%) had symptoms or conditions that would make them ineligible for product use *per labeling* but chose to purchase the product, and were allowed to do so. For example, among subjects who decided to purchase the product, a substantial number reported having a sense of incomplete bladder emptying (458 out of 1069 subjects or 43%), or stress incontinence (281 out of 1069 subjects or 26%). Of these, 323 and 198 subjects, respectively, used the product. It is likely that many of these subjects interpreted their symptoms as being responsive to Oxytrol.

A risk of diabetes was reported by 454 out of the 1069 subjects (42%), either because of a family history of diabetes, or because of a personal history of polydipsia and polyuria. Of these, 321 subjects used the product; only one case of diabetes was diagnosed during the course of the study. The majority of Advisory Committee members found it difficult to justify why a family history of diabetes would preclude one from safely using the product. As for subjects with as yet undiagnosed diabetes who were experiencing polydipsia and polyuria, it seemed unlikely that the product would mask their symptoms and lead to significant delays in diagnosis.

A total of 163 subjects (out of 1069, or 15%) reported symptoms consistent with a risk of bladder cancer. Of these, 100 subjects used the product. There were no cases of bladder cancer diagnosed during the study.

A total of 229 subjects (out of 1069, or 21%) reported symptoms consistent with a possible urinary tract infection; 154 of these used the product. Only 8 of these subjects were diagnosed with an infection over

the course of the study. Seven subjects recognized the symptoms or were diagnosed through routine care (by urinalysis at an office visit) and one subject was diagnosed based on the end-of-study urinalysis. In contrast, considering all 785 users who used at least one application of the product, 61 (or 8%) reported a urinary tract infection suggesting that most users with infections did not have classic symptoms of acute urinary tract infection. Among these 61 subjects, two reports were serious, requiring hospitalization and intravenous antibiotics; neither report involved sepsis or upper urinary tract complications.

Misuse. The CONTROL study met the protocol-specified primary endpoint. Misuse was defined as the proportion of all 785 users who developed new or worsening overactive bladder symptoms but who did not stop use and seek further medical evaluation. Potential reasons for misuse were further mitigated based on review of subject responses given during the planned interviews. The study found a mitigated misuse rate of 3.3% (95% CI: 2.2, 4.8), which is below the target threshold of 5%.

An exploratory analysis was also performed for the subgroup of 152 users who had new or worsening symptoms that should have led them to stop use and seek medical evaluation; among such users, 26 or 17% continued to use the product. Of note, the CONTROL study was not sufficiently powered to assess misuse in this subgroup. At the Advisory Committee meeting, some members expressed concern with use of the product beyond the labeled two weeks because of the potential for delayed diagnosis of other conditions with similar symptoms. Other members, however, were not as concerned with continued use of the product because extended use did not appear to be harmful.

Labeling. To ensure appropriate use of Oxytrol for Women in the OTC setting, the approved label will: 1) emphasize, through use of bold text that 2 or more overactive bladder symptoms should be present **for at least 3 months**, 2) state that the product should not be used if a doctor has diagnosed urinary or gastric retention, 3) delete reference to a family history of diabetes as a reason for ineligibility, and 4) direct the user to stop using the product and see a doctor if their condition does not improve after 2 weeks of use, if their condition worsens, or if new symptoms appear. In addition, the label will direct against use by men, and product packaging will be pink in color and depict a female silhouette to emphasize that the product is intended for use by non-pregnant women.

To address concerns raised by some Advisory Committee members that consumers should be informed about non-pharmacologic alternatives, a consumer information leaflet will be included in packaging to provide additional information about lifestyle changes and bladder retraining techniques that could help control overactive bladder symptoms and may be tried concurrently with Oxytrol for Women.

Product-related adverse effects. No new adverse effects related to the use of the oxybutynin transdermal system were identified either in the CONTROL study or in a comprehensive review of the global postmarketing experience with the product.

Anticholinergic adverse effects. Transdermal administration of oxybutynin bypasses first-pass gastrointestinal and hepatic metabolism, reducing the formation of the pharmacologically active N-desethyl metabolite. Despite this, several Advisory Committee members expressed concern regarding the potential for anticholinergic adverse effects with use of the product, especially among elderly users. To address this concern, the labeling for Oxytrol for Women will direct consumers to ask a doctor or pharmacist before using the product if they are taking a prescription medication for overactive bladder, or taking any drugs that may also cause sleepiness, dizziness, dry mouth, constipation or blurred vision. Labeling will also warn against driving or operating machinery until the subject knows how the product affects them; inclusion of this language is in accordance with recent revisions to the Warnings section of the prescription Oxytrol label that were approved on October 10, 2012.

Dermal carcinogenicity. A 24-month carcinogenicity study in rats at dosages of oxybutynin chloride of 20, 80, and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25, and 50 times the maximum exposure in humans taking an oral dose based on body surface area. Oxybutynin chloride is not mutagenic.

At the time of marketing approval of the prescription product, rodent studies evaluating dermal carcinogenicity of Oxytrol had not been performed, and there was no signal of application site neoplasm in subjects enrolled in the short-term clinical trials (or their extensions) that supported product approval. Any potential risk of application site neoplasm was further minimized by instructions in the product labeling to avoid re-application to the same site within a 7 day period. Since approval, there have been no signals of application site neoplasm in the global postmarketing experience with the product. During the review of this application, discussions involving DRUP, DNCE, the Executive Carcinogenicity Assessment Committee, and Dr. Susan Walker, Director of the Division of Dermatology and Dental Products, led to the conclusion that dermal carcinogenicity studies in rodents would not be required prior to the partial Rx-to-OTC switch of Oxytrol. Labeling for Oxytrol for Women will carry the same instructions to avoid re-application as provided in labeling for the prescription product.

Tradename Review

The applicant's proposed tradename "Oxytrol for Women" is acceptable from both a promotional and safety perspective.

Pediatric Considerations

The safety and effectiveness of Oxytrol for Women have not been established in subjects less than 18 years of age. The labeling for Oxytrol for Women will direct use to female consumers aged 18 years of age and older.

This partial Rx-to-OTC switch application does not trigger the pediatric study requirement under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), because it does not provide for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

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/s/

JULIE G BEITZ
01/24/2013