CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

SUMMARY REVIEW

Summary Review for Regulatory Action

Deputy Division Director/Cross-Discipline Team Leader Review

Date	January 26, 2009
From	George S. Benson, MD
Subject	Deputy Division Director/CDTL Review
NDA# **Supplement#**	22-204 S-000
Applicant	Watson Laboratories, Inc.
Date of Submission	March 27, 2008
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Proprietary Name/ **Established name**	Gelnique/ Oxybutynin chloride
Dosage forms/Strength	Transdermal gel/1 gram (100 mg oxybutynin) once daily
Proposed Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Recommendation	Approval

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1. Introduction

Overactive bladder (OAB) is a symptom complex which consists of urinary frequency and urgency incontinence. Anticholinergic drugs (muscarinic antagonists) have been a mainstay of OAB therapy for decades. The mechanism of action of these anticholinergic drugs is blockade of cholinergic (muscarinic) receptors in the bladder detrusor muscle and, therefore, inhibition of bladder contractility. The subject of this NDA (#22-204) review, oxybutynin chloride gel (Gelnique), is an anticholinergic drug proposed for the treatment of OAB.

Oxybutynin chloride (Ditropan) tablets were approved for the symptomatic treatment of OAB in 1975 and oxybutynin chloride syrup was approved for the same indication in 1979. Oxybutynin extended release tablets (Ditropan XL) were approved in 1998. A transdermal patch containing oxybutynin (Oxytrol TDS) was approved in 2003. The sponsor of Oxytrol TDS, Watson Laboratories, is also the sponsor of oxybutynin chloride gel. In addition to oxybutynin, currently approved oral agents in this drug class for the overactive bladder indication include tolterodine (Detrol), solifenacin (Vesicare), darifenacin (Enablex), trospium (Sanctura), and fesoterodine (Toviaz). Oxybutynin is the only drug available for the treatment of OAB in a transdermal formulation.

2. Background

Watson Laboratories, Inc. opened IND 67,126 [oxybutynin transdermal gel (OTG) for the treatment of OAB] on March 21, 2003. An End-of-Phase 2 meeting was held on August 2, 2005, during which the Division "highly recommended" two phase 3 studies to provide sufficient evidence of safety and efficacy for approval. The sponsor sought further guidance from the Division regarding the quantity of clinical data needed to support marketing approval in a follow-up teleconference held on November 4, 2005, during which the following were discussed:

1. To support marketing approval for the oxybutynin transdermal gel product, the sponsor planned to conduct one large phase 3 trial and to submit supportive evidence from comparative PK data.
2. Although the Division continued to recommend 2 confirmatory trials for the OAB indication, the Division also stated that "if confirmatory evidence exists, and no conflicting evidence exists, then a single study with a p-value ≤ 0.05 could be adequate to support approval of an NDA." The Division also stated that PK parameters must also be sufficiently similar.

The sponsor submitted the phase 3 protocol (Protocol OG05009) in June, 2006, but did not request a Special Protocol Assessment or the Division's comments. The Division concurred with the final statistical analysis plan for Study OG05009 in a letter dated September 20, 2007. A pre-NDA meeting was held with the sponsor on December 13, 2007, to discuss the submission of the NDA for oxybutynin transdermal gel (OTG).

3. CMC

The chemistry reviewer believes that "this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is now recommended for approval."

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer recommends approval. The reviewer notes: "The pharmacology and toxicology of oxybutynin have been well-characterized in numerous in vitro and in vivo studies. The excipients of the final formulation are either United States Pharmacopeia (USP), National Formulary (NF), or supported by respective Drug Master Files (DMF). The safety of transdermally administered oxybutynin has been well-established with Oxytrol. Because oxybutynin has been extensively studied, nonclinical investigations of Oxybutynin Transdermal Gel (OTG) were limited to in vitro human cadaver skin permeation studies to estimate a delivered dose, a primary skin irritation study in rabbits (Study ONY00012), a sensitization study in guinea pigs (Study ONY00013), and a light absorption test (ARD-RSR-0779) to evaluate phototoxicity potential. The battery of nonclinical studies did not demonstrate OTG to be irritating or sensitizing, and no significant absorbance of simulated sunlight was observed that would indicate a phototoxic potential. Clinical skin irritation and sensitization studies were also conducted."

5. Clinical Pharmacology

The clinical pharmacology reviewer finds "this NDA acceptable from a clinical pharmacology perspective." The reviewer concluded that the systemic exposure to oxybutynin, and the primary metabolite desethyloxybutynin, from the oxybutynin gel and the previously approved oxybutynin patch are similar. The clinical pharmacology reviewer further concluded that:

- Plasma oxybutynin and DEO concentrations and exposure of 1 g 10% OTG are similar to Oxytrol.
- Steady-state plasma levels of OTG for oxybutynin and DEO showed steady levels during a 24-hour period, consistent with transdermal delivery.
- Oxybutynin absorption of OTG is similar from the abdomen, thigh, and upper arm/shoulder application sites.
- Showering or sunscreen use with OTG application does not affect the overall systemic exposure to oxybutynin or its metabolism.
- OTG can be transferred between treated and untreated subjects through direct physical skin-to-skin contact, but this dermal transfer can be minimized by covering the application site with clothing.
- The population pharmacokinetics of OTG was similar to that observed in clinical pharmacokinetic studies.

6. Clinical Microbiology

The clinical microbiology reviewer recommends approval from the standpoint of product quality microbiology.

7. Efficacy/Statistics

In support of efficacy, the sponsor submitted the results of one large (789 patient), randomized, placebo-controlled trial (Study OG05009) and supportive pharmacokinetic data. Study OG05009 was a multicenter (76 United States sites), randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy and safety of 1 g 10% oxybutynin gel in the symptomatic improvement of OAB after 12 weeks of treatment. Eligible patients were randomized in a 1:1 ratio to either active (OTG group) or placebo gel (placebo group). Patients self-administered 1 g of gel daily to rotating sites on the abdomen, upper arms/shoulders, or thighs for 12 weeks during the 12 week double-blind period. A 14-week open-label safety extension period for approximately 200 patients from sites with the highest enrollment was added to the protocol of OG05009.

Inclusion/exclusion criteria:

The study population for Study OG05009 consisted of patients with a history of urge urinary incontinence and urinary frequency. Urinary symptoms were evaluated during screening by history and a 3-day urinary diary.

Key inclusion criteria included:

- men and women ≥ 18 years of age with a history of symptomatic overactive bladder with or without neurological disease
- average of ≥ 8 urinary voids per day and ≥ 4 urge urinary incontinence episodes per 3 days

- average urine void volume of ≤ 350 mL per void
- post-void urine residual ≤ 250 mL

Key exclusion criteria included:

- OAB symptoms related to chronic illness or anatomical weakness
- history of lower urinary tract surgery within the previous 6 months
- diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome

Efficacy Endpoints:

Primary endpoint:

- Change from baseline to 12 week endpoint in the double-blind period in the number of urinary incontinence episodes per day

Secondary endpoints:

Change from baseline to 12 week endpoint in the double-blind period in the following:

- average urinary frequency per day
- average urinary volume per void
- Incontinence Impact Questionnaire and the King's Health Questionnaire

Patient disposition:

Seven hundred eighty-nine (789 patients) were enrolled and randomized to treatment (400 to placebo and 389 to OTG). Of those randomized, 701 (89%) completed the 12-week double-blind period, with similar completion rates observed between the 2 treatment groups (89%). Eighty-eight (88) patients (11%) discontinued prematurely, primarily due to an adverse event (32 patients [4.1%]). More OTG-exposed patients discontinued because of an adverse event, whereas more placebo patients discontinued because of patient refusal/inability to participate further (Table 1).

Table 1: Subject Disposition in the Double-Blind Period

	Placebo N=400 n (%)	**OTG** N=389 n (%)	**Overall** N=789 n (%)
Completed	355 (88.8)	346 (88.9)	701 (88.8)
Discontinued	45 (11.3)	43 (11.1)	88 (11.2)
Discontinuation due to:			
* Adverse event	13 (3.3)	19 (4.9)	32 (4.1)
* Patient refusal/inability to participate further	17 (4.3)	13 (3.3)	30 (3.8)
* Lost to follow-up	8 (2.0)	9 (2.3)	17 (2.2)
* Protocol violation	3 (0.8)	1 (0.3)	4 (0.5)
* Investigator recommendation	2 (0.5)	0 (0.0)	2 (0.3)
* Other	2 (0.5)	1 (0.3)	3 (0.4)

Source: Study Report, Table 10-1, p. 52

Patient Demographics and Baseline Characteristics

The patient demographics and baseline characteristics are shown in Table 2.

Table 2: Patient Demographics and Baseline Characteristics (Double-Blind Period)

Variable	**Statistic**	**Placebo N=400**	**OTG N=389**
Age (years)	Mean (SD)	59.3 (12.2)	59.5 (12.5)
Female gender	n (%)	352 (88.0)	352 (90.5)
Geriatric ≥ 65 years old	n (%)	140 (35.0)	143 (36.8)
Ethnicity * Hispanic * Non-Hispanic	 n (%) n (%)	 25 (6.3) 375 (93.8)	 18 (4.6) 371 (95.4)
Race * White * Black * Asian * Others	 n (%) n (%) n (%) n (%)	 335 (83.8) 54 (13.5) 7 (1.8) 4 (1)	 346 (88.9) 33 (8.5) 6 (1.5) 4 (1)
BMI (kg/m^2)	Mean (SD)	31.5 (8.0)	31.0 (7.2)
Duration of Incontinence (months)	Mean (SD) Median	97.4 (98.9) 60.0	106.6 (121.6) 60.0
Previous/current OAB medical treatment	n (%)	109 (27.3)	91 (23.4)

Source: Study report, Table 11-2, p. 56

Most patients were non-Hispanic white women (approximately 90%) with a mean age of 60 years. Approximately 40% of participants were at least 65 years old and had a mean duration of incontinence of 107 months. Approximately 27% of patients had received previous medical treatment for OAB. The drug and placebo groups were balanced with respect to demographics and baseline characteristics.

Efficacy:

The primary efficacy endpoint was change from baseline to week 12 in the double-blind period in the number of urinary incontinence episodes per day (treatment compared to placebo). The mean (5.4) and median (4.7) number of daily incontinence episodes at baseline were identical for the 2 treatment groups. At endpoint, the mean change from baseline incontinence episodes per day was -3.0 for the oxybutynin gel (OTG) group (56% improvement) and -2.5 for the placebo group (46% improvement). The mean difference between the active and placebo groups was -0.51 incontinence episodes per day and this difference was statistically significant ($p < 0.0001$). (See Table 3).

Table 3: Urinary Incontinence Episodes per Day (mITT)

	Statistic	**Placebo N = 400**	**OTG N = 389**
Baseline	Mean (SD) Median	5.4 (3.3) 4.7	5.4 (3.3) 4.7
Change from baseline to Endpoint (LOCF)	**Mean (SD)** Median **Mean difference (95% CI)** **p-value**	**-2.5 (3.1)** -2.0	**-3.0 (2.7)** -2.7 **-0.5 (-0.14,-0.88)** **<0.0001***

*Versus placebo comparing least squares adjusted means
Source: Study report, Tables 14.2.1-1, 2, p. 178-9

The agreed upon primary analysis population was the mITT population utilizing last observation carried forward (LOCF). The mITT population included all randomized patients who received at least one dose of study drug and provided data for the baseline efficacy assessment. In the case of misrandomization, the actual treatment given was to be used in the summary statistics and data analysis. The ITT population was a secondary efficacy analysis population and was defined the same as the mITT population, except that in the case of misrandomization, the randomized treatment was to be used in the summary statistics and data analysis. The results using the ITT population were similar to those obtained with the mITT population.

The treatment effect of oxybutynin gel (mean treatment difference from placebo of -0.5 episode/day) is comparable to that observed with other approved OAB products, including Oxytrol TDS. The placebo response was significant in OG05009 (46% improvement from baseline), as seen in other clinical OAB trials. No adequate trials have been performed which compare the efficacy of oxybutynin gel to other anticholinergic drugs approved for the treatment of OAB.

The secondary endpoint of change from baseline to endpoint (Week 12, LOCF) in daily urinary frequency is an important endpoint which has been labeled for other anticholinergic drugs, including Oxytrol TDS, which have been approved for the OAB indication. The mean baseline urinary frequency per day was similar between the placebo and OTG groups (approximately 12 micturitions per day). At endpoint, the mean change from baseline in daily urinary frequency was -2.0 micturitions for the placebo group and -2.7 micturitions for the OTG group. The mean difference between active and placebo groups was -0.7 micturition per day and this difference was statistically significant (p = 0.0017). (See Table 4).

Table 4: Daily Urinary Frequency (mITT, LOCF)

	Statistic	**Placebo N = 400**	**OTG N = 389**
Baseline	Mean (SD) Median	12.2 (3.3) 11.3	12.4 (3.3) 11.7
Change from baseline to Endpoint	**Mean (SD)** Median p-value	**-2.0 (2.8)** -1.7	**-2.7 (3.2)** -2.7 **0.0017***

*Versus placebo comparing least squares adjusted means
Source: Study report, Tables 11-7, p. 63

Although no adequately designed trials have compared the urinary frequency treatment effect of oxybutynin gel with other anticholinergic drugs approved for the treatment of OAB, the mean treatment effect of OTG on urinary frequency appears to be similar to other approved drugs, including Oxytrol TDS.

An additional secondary endpoint in Trial OG05009 was change from baseline to endpoint (Week 12, LOCF) in average volume voided per micturition. The mean (approximately 165 mL) baseline urinary volume per void was similar between the placebo and OTG groups. At endpoint, the mean change from baseline in average volume voided per micturition was +3.8 mL for placebo and +21.0 mL for OTG. The mean difference between active and placebo groups was +17 mL and this difference was statistically significant (p = 0.0018).

Statistical review:

The statistical reviewer concluded:

"The one submitted study provides statistically supportive evidence demonstrating the efficacy of 1 g of 10% Oxybutynin Topical Gel once daily for the treatment of overactive bladder with symptoms of urgency, urge incontinence, and urinary frequency.

From a statistical perspective, the sponsor provided adequate data to support the efficacy of 1 g 10% Oxybutynin Topical Gel once daily for the treatment of overactive bladder symptoms based on the number of daily incontinence episodes. We also recommend that labeling not include p-values for the secondary endpoints because no adjustment for multiplicity was pre-specified in the protocol."

The inclusion of p-values in the label for the secondary endpoints of urinary frequency and average volume voided per micturition was further discussed with the statistical review team and with the sponsor. Because all of the previously approved anticholinergic drugs for the OAB indication have p-values for these two endpoints in labeling and because the changes remain statistically significant following adjustment for multiplicity, p-values for the changes in the secondary endpoints of urinary frequency and average volume voided per micturition will be included in labeling.

Efficacy Conclusions:

The results of the primary Study OG05009 demonstrated that OTG treatment resulted in highly statistically significant improvement in the primary endpoint (urinary incontinence episodes) and the key secondary endpoints (urinary frequency and urine volume per void) compared to placebo at 12 weeks. Although no adequately designed trials have compared the efficacy of OTG to other approved anticholinergic drugs for the treatment of OAB, the efficacy results appear to be similar. Supportive PK data demonstrate that the AUC, C_{avg}, and C_{max} values for oxybutynin and the primary metabolite desethyloxybutynin are similar for OTG and Oxytrol.

8. **Safety**

The following sources were reviewed for safety assessment by the primary medical officer:

1. Integrated summary of safety (ten phase 1 studies and one phase 3 study [OG05009]). The safety review relies primarily on the findings of Study OG05009, especially on the data from the double-blind period of OG05009.
2. Three non-integrated studies (two dermatoxicity studies and one person-to-person transference study). The 3 studies were not integrated for the following reasons: the cumulative irritation study evaluated the "worst case" local tolerance scenario, the skin sensitization study used 50% of the therapeutic dose, and subjects applying OTG in the transference study were monitored for only 4 hours post-dose.
3. Annual reports of Oxytrol TDS and IND 67,126 and the 120-day Safety Update.
4. Published literature and approved anticholinergic OAB product labels.

Extent of Exposure:

In total, NDA 22-204 contains safety data from 1033 subjects who received at least one dose of OTG. These subjects included 496 OAB patients in the integrated phase 3 study (double blind and open-label portions of the study), 216 healthy subjects in the integrated phase 1 studies, and 296 healthy subjects in the non-integrated phase 1 studies.

In trial OG05009, 496 patients (389 randomized to active OTG in the double-blind period plus 107 randomized to placebo in the DB period and who received active OTG during the open-label period) were exposed to 1 g 10% OTG for an average of 103 days (range 1-227 days). One hundred-nine (109) patients received > 12 weeks of active treatment; 71 patients completed 26 weeks of treatment. In the double-blind period, the mean (SD) duration of exposure was 81.5 (20.4) days for placebo and 81.6 (19.4) days for the active OTG group. In the open-label period, the mean exposure to OTG was 89.9 days (range 1-142 days).

Deaths:

One death occurred in the entire safety database. A 54-year-old woman in the skin sensitization study (OG05004) received 4 applications of 0.5 g 10% OTG prior to being lost to follow-up. In attempting to contact the subject, the sponsor discovered that she died from causes related to alcoholism (alcohol blood level of 0.09%, ketoacidosis, and gastrointestinal bleed), according to a medical examiner's autopsy report. The death was not considered to be treatment-related, and the primary medical officer and I agree.

Serious adverse events (SAE's):

In the entire safety database, 17 patients reported a total of 18 SAE's (7 OTG patients [1.8%] reported 7 SAE's, and 10 placebo patients [2.5%] reported 11 SAE's). All SAE's occurred in the double-blind portion of the phase 3 study. SAE's in the OTG group were non-cardiac chest pain, multiple myeloma, enlarging ovarian adenoma, atrial fibrillation, pneumonia, cerebral infarction, and osteoarthritis. Serious adverse events in the placebo group included atrial fibrillation, labyrinthitis, urosepsis, dizziness, vertigo, abdominal pain upper, gastrointestinal inflammation, joint dislocation, foot fracture, renal hemorrhage, and orthostatic hypotension. Seven patients discontinued the study due an SAE: 3 patients in the OTG group (1 each from an enlarging ovarian adenoma, atrial fibrillation, and cerebral infarction) and 4 patients in the placebo group (1 each from atrial fibrillation, labyrinthitis, vertigo/near syncope, and joint dislocation). Other than vertigo, all SAE's leading to study drug discontinuation resolved. None of the SAE's was considered treatment-related. No non-fatal SAE's occurred in the healthy volunteer phase 1 studies.

The primary medical officer reviewed all of the SAE case narratives and did not consider any SAE to be treatment-related.

Patient disposition in trial OG05009:

- Double-blind period: 19 of 389 OTG patients (4.9%) and 13 of 400 placebo patients (3.3%) discontinued treatment due to an adverse event. The primary reasons for discontinuations were headache (4 patients in OTG [1%], 5 in placebo [1.25%]), followed by application site reactions (3 patients in the OTG group [0.8%]; 1 patient in the placebo group [0.25%]). The incidence of discontinuation due to a treatment-related adverse event, or adverse reaction, was identical between active and placebo groups (1.8%).
- Open-label period: 15 of 216 patients (6.9%) discontinued prematurely due to an adverse event. A majority of patients (9 patients, 4.1%) discontinued because of an application site reaction. These application site reactions were pruritis (4 patients), dermatitis (3 patients), dryness (3 patients), erythema (2 patients), pustules (2 patients), discoloration (1 patient), and papules (1 patient). The number of listed adverse events exceeds nine because a single patient could have experienced more than one application site reaction.

The adverse reactions leading to patient discontinuation in the double-blind and open label portions of study OG05009 are shown in Table 5.

Table 5: Adverse Reactions Leading to Discontinuation in Phase 3 Study (Both Double-Blind and Open-Label Portions of the Study) (Medical Officer's Analysis)

Preferred Term	**OTG* N=496 n[+] (%)**	**Placebo N=400 n (%)**
Application site dermatitis	4 (0.8)	0
Application site pruritis	4 (0.8)	1 (0.2)
Application site pustules	2 (0.4)	0
Headache	2 (0.4)	3 (0.6)

**Includes patients who completed 12 weeks of placebo treatment and entered the open-label period*
+One patient may report more than one type of application site reaction.

Common adverse reactions:

Common adverse reactions reported in the double-blind phase of study OG05009 are shown in Table 6.

Table 6: Common Adverse Reactions (≥ 1% in OTG group) in Double-Blind Portion of Phase 3 Study

Preferred Term	**OTG N=389 n (%)**	**Placebo N=400 n (%)**
Any adverse reaction	**73 (18.8)**	**45 (11.3)**
Dry mouth	27 (6.9)	11 (2.8)
Any application site reaction	21 (5.4)	4 (1.0)
Application site pruritis	8 (2.1)	3 (0.8)
Application site dermatitis	7 (1.8)	1 (0.3)
Headache	6 (1.5)	11 (2.8)
Dizziness	6 (1.5)	2 (0.5)
Constipation	5 (1.3)	4 (1.0)
Pruritis	5 (1.3)	5 (1.3)

Source: Study report, Table 12-5, p. 80

The common adverse reactions seen with OTG are consistent with those seen with other approved anticholinergic drugs.

Patient subgroups of age and race:

In phase 3 study OG05009, no significant differences in the incidence or frequency of adverse events were noted between patients older and those younger than 65 years of age. Because a majority of the patients were non-Hispanic, White females (80-90%), no meaningful conclusions can be drawn with regards to gender or ethnicity.

Laboratory abnormalities:

A review of the summary of clinically significant changes in clinical laboratory parameters showed a discrepancy between the OTG and placebo groups in the incidence of liver function test (LFT) abnormalities. In the 74-Day letter, the Division requested that the sponsor submit analyses of LFT outliers meeting certain outlier thresholds (e.g., ALT ≥ 3X ULN, 5X ULN; AST ≥ 3X ULN, 5X ULN; bilirubin ≥ 2X ULN) and a summary of all AE's related to LFT changes. The sponsor responded to this request in an amendment to the NDA (Amendment 004 dated August 27, 2008). The primary medical officer also evaluated the LAB.xpt dataset to assess how many subjects had outlier LFT values during the double-blind treatment period and in the overall phase 3 study and used these data to populate Tables 7 and 8.

The number of patients with significant LFT outlier values during the double-blind treatment period are shown in Table 7.

Table 7. Number of LFT outliers during the double-blind treatment period.

LFT parameters	**OTG N=389 n (%)**	**Placebo N=400 n (%)**
ALT or AST > 3X and < 5X ULN	2 (0.5)	3 (0.7)
ALT or AST > 5X ULN	3 (0.8)	0
Bilirubin > 2X ULN	0	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	0

*Outlier values were observed at Week 7/ET

The number of patients who were LFT outliers during both the double-blind and open-label portions of phase 3 trial OG05009 is shown in Table 8. The OTG group contains patients who were enrolled in both the double-blind and open-label portions of phase 3 trial OG05009.

Table 8. Number of patients with outlier LFT values during the entire phase 3 study (double-blind and open-label portions)*

LFT parameters	**OTG N=496 n (%)**
ALT or AST > 3X and <5X ULN	4 (0.8%)
ALT or AST > 5X ULN	4 (0.8%)
Bilirubin > 2X ULN	1
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0

*Outlier values were observed at Week 7/ET or Week 9/ET. Patients receiving placebo in the double-blind period who entered the open-label period and experienced an outlier value were included in the OTG group denominator.

Subjects who were considered to be LFT outliers for both portions of the study are further described in Table 9.

Table 9. Subjects meeting or exceeding outlier LFT thresholds in both the double-blind and open-label portions of study OG05009

Table 1 Summary of Patients Meeting Defined Threshold Laboratory Values

Pt ID (treatment)	Screening	Visit 7 (Double-blind Week 12)	Visit 9 (Open-label Week 26)
10401 (active)	*	ALT, GGT	**
10928 (active)	*	ALT, AST, GGT	**
12626 (placebo)	*	*	AST
13316 (active)	bilirubin	*	bilirubin
14520 (active)	*	ALT, AST, GGT	*
15322 (placebo)	*	ALT, GGT	ALT, AST, GGT
15334 (active)	*	ALT, GGT	**
16110 (active)	ALT, GGT	*	ALT, GGT
16217 (placebo)	creatinine	creatinine	*
17317 (placebo)	GGT	ALT	**
19110 (active)	ALT, GGT	ALT, GGT	**

Threshold values: AST, ALT, GGT = 3X or 5X ULN; creatine and bilirubin = 2X ULN

Notations in red indicate value > 5x ULN

* = test did not meet predefined threshold values ** = did not participate in open-label period

One OTG patient had a bilirubin > 2X ULN at the end of the open-label period of trial OG05009. Subject 13316 was randomized to active treatment in the double-blind period and entered and completed the open-label period. The subject had a baseline bilirubin level of 2.0, which decreased to 1.5 at Visit 7 (Week 12), and increased back to a level of 2.1 at Visit 9 (Week 26). The primary medical officer believes that it is unlikely that the subject's hyperbilirubinemia was drug-related and I agree. The subject did not have liver transaminase (ALT, AST), GGT, or alkaline phosphatase elevation at any time during the study.

The primary medical officer also evaluated the number of patients with bilirubin > 1.5X ULN. In all, 5 of 496 OTG-exposed patients (1%) and 3 of 400 placebo patients (0.75%) had bilirubin levels > 1.5X ULN at the end of the study. All of these 8 patients also had baseline bilirubin values > 1.5X ULN that were similar to their end of treatment values.

Of the 8 patients who received at least one dose of OTG and who had elevations in ALT or AST values > 3X ULN post-randomization, only 2 had normal baseline AST and ALT values (Subjects 10928 and 12626). Three subjects (Subjects 10928, 14520, and 15322) had AST and ALT elevations > 3X ULN. No patient had concurrent elevations of bilirubin and AST/ALT.

The four patients with ALT or AST >5X ULN are discussed in the primary medical officer review (pages 57-59). Patient 14520 had a history of hepatitis C and had elevated LFT's at baseline. Her ALT and AST approximately doubled while on study drug and then normalized when drug was discontinued. Patient 15322 also had elevated LFT's at baseline. Patient 10401 had slightly elevated LFT's at baseline and was taking multiple medications including Vicodin during the trial. Patient 10928 had a slightly elevated GGT at baseline and her concomitant medications included rosuvastatin. None of these patients had elevated bilirubin levels at baseline or at any time during the trial.

Two patients prematurely discontinued the open label safety extension because of liver function test elevations. Both of these patients had received active OTG treatment during the double-blind period. Both had significantly elevated LFT's at baseline and both experienced increases while on drug therapy. Drug was discontinued and the increased LFT's returned to baseline levels. Neither patient had an elevated bilirubin at any time during the trial.

With regard to the LFT issue, the primary medical officer concluded that:

- There was a slight excess of OTG-exposed patients compared to placebo who had ALT/AST elevations exceeding the 3X ULN and 5X ULN limits. None of these patients had an increased bilirubin associated with the ALT/AST elevation.
- Drug-causality could not be completely excluded in the 4 OTG-exposed patients who had ALT/AST elevations > 5X ULN (discussed above). However, all of these patients also had other plausible reasons for LFT elevations (e.g., concurrent medications and/or diseases). Three of the four patients had elevated ALT/AST and one had an elevated GGT at baseline.
- With the extent of exposure to oxybutynin during the past 34 years and the known systemic safety profile of oxybutynin, it is unlikely that OTG has significant potential of causing severe drug-induced liver injury.

I agree with the conclusion that it is highly unlikely that OTG has significant potential to cause drug-induced liver injury.

Skin safety:

During the double-blind treatment period of Study OG05009, three patients in the OTG group (0.8%) and one patient in placebo group (0.3%) discontinued the trial because of an application site reaction. During the open label period, 9 patients (4.2%) discontinued because of an application site reaction. These application site reactions were pruritis (4 patients) dermatitis (3 patients), dryness (3 patients), erythema (2 patients), pustules (2 patients), discoloration (1 patient), and papules (1 patient). The incidence of discontinuation because of an application site reaction was higher for patients exposed to ≥ 12 weeks of treatment (3.7%) compared to those exposed < 12 weeks (2.1%).

None of the application site reactions in the double-blind phase of study OG05009 were considered to be severe. During the open label phase of the trial, two of the nine patients who discontinued the trial because of an application site reaction were judged to have severe application site reactions consisting of dermatitis, urticaria, and erythema.

Study OG05003 (21-day cumulative skin irritation study): This was a 21-day, double-blind, placebo-controlled study in 45 healthy male and female subjects. Active and placebo gel (1 g 10% OTG and 1 g placebo gel) were applied daily (each subject received both test gels applied to opposite sides of the back) by site personnel. Each application site was covered with gauze for 24 hours prior to the next application. Dermatologic examination was conducted at baseline, at the time of each gauze removal, and 24 hours after the final gauze removal. A score was assigned when ≥ 25% of the application site

demonstrated a skin reaction or when a clinically significant skin response was noted. The irritation potential of the test gels was evaluated in terms of cumulative irritation. Both active and placebo gels produced Class 1 irritation scores indicating "essentially no evidence of cumulative irritation under conditions of test." The normalized (Base 10) cumulative irritation score of active gel was 34.88 and that of placebo was 23.66; scores of 0-50 was considered as Class 1 irritation score.

Study OG05004 (skin sensitization study): The 1 g dose of 10% OTG was not used in this study; instead 0.5 g 10% OTG was used. This was a 21-day, double-blind, placebo-controlled study in 225 healthy male and female subjects. The objective of this study was to evaluate the incidence of contact sensitization following repetitive applications of active OTG and placebo gel. In the induction phase, study personnel applied 0.5 g active and 0.5 g placebo gel (the same subject received both types of test gels on opposite sides of the back) three times per week for 21 days (total of 9 applications of each test gel). The contact time for each application was 24 hours. A rest period of 2 weeks followed the induction phase. In the challenge phase, a single 48-hour "challenge" application was made using placebo and active gel on each subject with evaluations within 5 minutes, 24, 48, and 72 hours after gauze removal. Test gels were applied to the same sites each time unless significant irritation developed.

One subject (0.5%) was sensitized to OTG. Subject 1087 had mild erythema with papules at each evaluation of the active OTG application site during the challenge phase. During re-challenge, the subject had mild erythema with papules on the OTG application site at 5-minutes, 24-hours, 48-hours, and 72-hours after gauze removal.

The potential of skin hypersensitivity to OTG will be labeled in the WARNINGS and PRECAUTIONS section of the label.

Person-to-person transference

Study OG06007: This was a single-dose, open-label, randomized, parallel group study to evaluate the potential of dermal transfer of OTG from a treated person to an untreated person. Fifty-two healthy male and female subjects were randomized to either a single dose of 1 g 10% OTG applied to the abdomen (treated) or no treatment (untreated). The treated group was further randomized to cover the application site with clothing or no cover in a 1:1 ratio. At one hour post-application, treated and untreated partners had direct physical contact at the application site for 15 minutes. Oxybutynin PK parameters were assessed in the untreated partners at 0, 2, 4, 8, 12, 24, 36 and 48 hours after contact.

All untreated partners not protected by clothing had detectable plasma concentrations of oxybutynin (mean C_{max} = 0.94 ng/mL, mean $AUC_{[0\text{-}48\ hrs]}$ = 29.78 ng.h/mL). Plasma concentrations of oxybutynin increased from 2-8 hours post-dose and were still detectable at 48 hours post-dose. Twelve of the 14 untreated subjects whose partner covered the application site with clothing had no measurable blood levels of oxybutynin, whereas the remaining 2 untreated subjects showed trace levels (mean C_{max} =0.02 ng/mL) starting at 8 hours post-dose and which were still detectable at 48 hours post-dose.

The risk of transference of oxybutynin to an untreated partner via direct skin-to-skin contact and the minimization of this risk by covering the application site with clothing will be addressed in the WARNINGS and PRECAUTIONS section of the label.

Safety summary:

The safety profile of OTG is overall acceptable. The expected anticholinergic systemic effects of a transdermal oxybutynin product were seen in Trial OG05009 and can be adequately labeled. Contact hypersensitivity to OTG reactions occurs at an incidence of 0.5%. Contact hypersensitivity will be included in the WARNINGS and PRECAUTIONS section of the label. Direct skin-to-skin contact at the application site of OTG results in oxybutynin dermal transfer to the untreated partner to a variable extent. This risk can be minimized with protecting the application site with clothing and this information will be included in the WARNINGS and PRECAUTIONS and PATIENT COUNSELING INFORMATION sections of the label.

9. Advisory Committee Meeting

There are currently six anticholinergic (antimuscarinic) drugs approved for the treatment of overactive bladder. Oxybutynin was first approved in tablet form in 1975. A transdermal patch containing oxybutynin (Oxytrol TDS) was approved in 2003. The efficacy of oxybutynin gel appears to be comparable to the other approved drugs in its class and no new safety concerns were identified. No advisory committee was convened.

10. Pediatrics

The sponsor requested a pediatric waiver (0-4 years old) and pediatric deferral (5-16 years old).

The sponsor's pediatric plan was presented to the Pediatric Review Committee (PeRC) on two occasions. The following pediatric plan was acceptable to PeRC and was discussed with the sponsor:

- A pediatric waiver will be granted for OTG in children from birth to 5 years, 11 months of age.
- A pediatric deferral will be granted for children aged 6 years to 16 years, 11 months.
- The patient population to be studied under the sponsor's pediatric plan is children aged 6 years to 16 years, 11 months, with urinary signs and symptoms related to neurologic disease.

11. Other Relevant Regulatory Issues

a. Division of Scientific Investigations (DSI):

The Division of Scientific Investigations inspected 2 large study centers (Dr. Leah Schmidt-24 patients; Dr. Harry Deeths-35 patients) that participated in Study OG05009. The inspections of the study conduct and data management did not reveal significant discrepancies or regulatory violations. DSI concluded that the data inspected "appear acceptable in support of the respective application."

b. Office of Surveillance and Epidemiology (OSE)

- Division of Medication Error Prevention and Analysis (DMEPA):

  DMEPA found the tradename "Gelnique" acceptable. The review of the container/carton labels is completed and DMEPA also finds them to be acceptable.

- Division of Risk Management (DRISK):

  DRISK's recommendations have been incorporated into the Patient Information portion of labeling.

c. Study Endpoints and Labeling Development Team (SEALD):

A consultation from SEALD regarding the label (in Physician's Labeling Rule format) was obtained and recommended changes were incorporated into labeling.

d. Division of Drug Marketing, Advertising, and Communications (DDMAC):

The majority of DDMAC's recommendations were incorporated into the labeling which was negotiated with the sponsor.

e. Financial Disclosure:

Appropriate financial disclosure forms were submitted. Financial disclosure documents were submitted only for clinical investigators (principal and sub-investigators) for Study OG05009; this approach is acceptable, because the approval of this NDA is based primarily on Study OG05009.

A total of 76 investigators and 175 sub-investigators from 76 study sites had no disclosures in the categories of compensation potentially affected by the outcome of the covered study, proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product, or significant payments of other sorts from the sponsor of the covered study. There was no missing financial disclosure information for investigators of Study OG05009.

In summary, the sponsor submitted adequate information to demonstrate compliance with financial disclosure requirements.

12. Labeling

Label negotiations were completed with the sponsor on January 21, 2009. The label is in the Physician's Labeling Rule (PLR) format.

13. Decision/Action/Risk Benefit Assessment

The results of the single, large, adequately controlled Study OG05009 demonstrated that OTG treatment resulted in statistically significant improvement in the primary endpoint (urinary incontinence episodes) and the key secondary endpoints (urinary frequency and urine volume per void) compared to placebo at 12 weeks. Although no adequately designed trials have compared the efficacy of OTG to other approved anticholinergic drugs for the treatment of OAB, the efficacy results seen with OTG appear to be similar. Supportive PK data demonstrate that the AUC, C_{avg}, and C_{max} values for oxybutynin and desethyloxybutynin are similar for OTG and Oxytrol.

The safety profile of OTG is overall acceptable. The expected anticholinergic systemic effects of a transdermal oxybutynin product were seen in Trial OG05009 and can be adequately labeled. Contact hypersensitivity to OTG reactions occurs at an incidence of 0.5%. Contact hypersensitivity will be included in the WARNINGS and PRECAUTIONS section of the label. Direct skin-to-skin contact at the application site of OTG results in oxybutynin dermal transfer to the untreated partner to a variable extent. This risk can be minimized with protecting the application site with clothing and this information will be included in the WARNINGS and PRECAUTIONS and PATIENT COUNSELING INFORMATION sections of the label.

The risk/benefit assessment of OTG favors approval of NDA 22-204. I agree with the primary medical officer and the CMC, pharmacology/toxicology, clinical pharmacology, and statistical reviewers that NDA 22-204 should be approved. Label negotiations are completed. No post-marketing studies other than those required by PREA (Pediatric Research Equity Act) for pediatric patients are necessary (see Section 10. Pediatrics of this review). There are no outstanding issues regarding the approval of this NDA submission.

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/s/

George Benson
1/26/2009 06:05:26 PM
MEDICAL OFFICER