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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Oxybutynin chloride
(Proposed) Trade Name	Gelnique
Therapeutic Class	Antimuscarinic
Applicant	Watson Laboratories, Inc.
Priority Designation	S
Formulation	Transdermal gel
Dosing Regimen	1 g once daily (100 mg oxybutynin)
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Intended Population	Adults with overactive bladder
Related IND's/NDA's	67,126 (Oxybutynin Transdermal Gel) 50,489 (Oxytrol TDS) NDA 21-351 (Oxytrol TDS)

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

From a clinical perspective, Oxybutynin Transdermal Gel 10% 1 gram applied once daily should be approved for the indication of "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency" in adults with overactive bladder.

This recommendation is based on the demonstration of "substantial evidence" of effectiveness in improving symptoms of overactive bladder in the target population and an acceptable safety profile.

1.2 RECOMMENDATION ON POSTMARKETING ACTIONS

No new safety concerns have been identified which require actions other than routine postmarketing surveillance.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

Oxybutynin has been approved for the symptomatic treatment of overactive bladder (OAB) since 1975. It is a tertiary amine that is thought to exert its therapeutic effects by muscarinic receptor blockade of the M3 receptor subtypes that predominate in the bladder and are thought to mediate detrusor contractibility. Oxybutynin exists commercially as a racemic mixture of R- and S-enantiomers (R-OXY, S-OXY). In-vivo and animal studies have been conducted with conflicting results regarding whether the pharmacological effects and anticholinergic activities of racemic oxybutynin are attributable primarily to the R or S isomer.[1,2]

The continued use of and patient compliance with oxybutynin treatment have been limited by anticholinergic side effects, such as dry mouth and constipation. The sponsor developed a transdermal matrix formulation of oxybutynin (Oxytrol Transdermal System, or Oxytrol TDS) in an attempt to improve the tolerability profile of oxybutynin. Unlike oral administration, transdermal delivery of oxybutynin avoids the first-pass metabolism resulting in decreased conversion of oxybutynin to N-desethyloxybutynin (DEO), a major active metabolite thought to contribute significantly to the anticholinergic side effects of oxybutynin. The transdermal delivery system is thought to result in an improved tolerability profile and better patient compliance. The primary disadvantage of the oxybutynin transdermal matrix delivery system, however, is application site reactions. In controlled clinical trials for Oxytrol TDS, approximately 16-21% of patients reported application site reactions, and approximately 10% of patients discontinued therapy because of these reactions. Oxytrol TDS (3.9 mg/day), an occlusive matrix-type transdermal patch, was approved for the symptomatic treatment of overactive bladder in 2003.

The sponsor developed oxybutynin transdermal gel (OTG) as a second generation product for Oxytrol TDS. An un-occluded gel system was considered to have better skin tolerability than the occlusive Oxytrol TDS. The clinical development plan focused on defining an OTG formulation and dose that would provide blood levels and exposures of oxybutynin and DEO similar to Oxytrol TDS (3.9 mg/day). The proposed dose is one sachet containing 1 g of 10% oxybutynin gel once daily with no specific dose adjustments for specific populations. The data to support the safety and efficacy of 1 g OTG 10% came from one large, multicenter, randomized, double-blind, and parallel group study of 12 weeks duration

followed by a 14-week open-label extension in 789 adult men and women with overactive bladder (Study OG05009).

The sponsor seeks approval of 1 g 10% OTG for the "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." OTG has not been approved for marketing in any country.

***Reviewer's comment**: During the teleconference held on November 2, 2005, the Division stated that a single safety and efficacy study with $p \leq 0.05$ could be adequate to support approval of an NDA, provided that confirmatory evidence exists, no conflicting evidence exits, and the PK data are sufficiently supportive. In the clinical development of OTG, clinical efficacy was evaluated only in one clinical study (OG05009) using one drug dose.*

1.3.2 Efficacy

The **primary efficacy endpoint** in Study OG05009 was change from baseline to Endpoint (Week 12, LOCF) in the number of urinary incontinence episodes per day recorded in the 3-day urinary diary in the 12-week double-blind study period. Currently, this endpoint is an accepted primary endpoint in phase 3 clinical trials evaluating treatment of symptomatic OAB. Compared to placebo, OTG treatment resulted in statistically significant improvement in the number of daily urinary incontinence episodes. At baseline, the mean (5.4) and median (4.7) numbers of urinary incontinence episodes per day were identical for both treatment groups. At Endpoint (Week 12, LOCF), the mean change from baseline in the number of daily urinary incontinence episodes was -3.0 for the OTG treatment group and -2.5 for the placebo group. The mean difference in the primary endpoint between the OTG and placebo groups was -0.5 episodes per day (95% CI: -0.14, -0.87), and this difference was statistically significant ($p < 0.0001$). The study was powered to detect a difference of -0.52 incontinence episodes per day between the 2 study groups and this anticipated mean difference was achieved at Endpoint. Statistically significant improvement in urinary incontinence associated with OTG treatment was observed starting at Week 4 and maintained to Week 12. See Table 1.

Table 1: Change from Baseline Incontinence Episodes per Day (mITT)

Visit	Statistics	Placebo	OTG
Baseline	N Mean (SD) Median	400 5.4 (3.3) 4.7	389 5.4 (3.3) 4.7
Week 1 (OC)	N Mean (SD) Median p-value*	390 -1.8 (2.6) -1.3	384 -2.0 (2.4) -1.7 0.18
Week 4 (OC)	N Mean (SD) Median p-value*	374 -2.3 (2.9) -2.0	366 -2.7 (2.6) -2.3 **0.0004**
Week 8 (OC)	N Mean (SD) Median p-value*	359 -2.5 (2.9) -2.0	354 -3.0 (2.6) -2.7 **0.0002**
Week 12 (OC)	N Mean (SD) Median p-value*	358 -2.6 (3.1) -2.3	348 -3.0 (2.8) -2.7 **0.0004**
Week 12 (LOCF)	N Mean (SD) Median p-value*	400 **-2.5** (3.1) -2.0	389 **-3.0** (2.7) -2.7 **<0.0001**

*Versus Placebo comparing least squares adjusted means
Source: Module 2.7.3, Summary of Clinical Efficacy, p. 15-16

The 2 major **secondary endpoints** were changes from baseline in daily urinary frequency and in the average volume per void.

Daily urinary frequency: At baseline, the mean (OTG: 12.4, placebo: 12.2) and median (OTG: 11.7, placebo: 11.3) daily urinary frequency were similar between the OTG and placebo groups. Compared to placebo, OTG treatment resulted in statistically significant improvement in daily urinary frequency at Endpoint (p=0.0017). At Endpoint, the mean change from baseline in daily urinary frequency was -2.7 episodes for the OTG group compared to -1.7 episodes for the placebo group.

Average urine volume per void: At baseline, the mean (OTG: 163 mL, placebo: 168 mL) and median (160 mL for both treatment groups) average urine volume per void were similar between the OTG and placebo groups. Compared to placebo, OTG treatment resulted in a statistically significant increase in the average urine volume per void at Endpoint (p=0.0018). At Endpoint, the mean change from baseline in the average urine volume per void was +21.0 mL for the OTG group compared to +3.8 mL for the placebo group.

The improvement in the number of daily urinary incontinence episodes with OTG treatment was clinically and statistically meaningful. The improvements in daily urinary frequency and average urine volume per void were statistically significant and consistent with the primary result. Although there is no

comparative efficacy trial of the two transdermal oxybutynin products, the improvements in the key efficacy endpoints appear to be comparable between 1 g 10% OTG and Oxytrol TDS (3.9 mg/day).

1.3.3 Safety

Safety data were based on a total of 1033 subjects who received at least one dose of OTG. These subjects were enrolled in 14 completed trials, 13 of which were conducted in the U.S. The 1033 subjects included 496 OAB patients in the integrated phase 3 study (double blind and open-label), 216 healthy subjects in the integrated phase 1 studies, and 296 healthy subjects in the non-integrated phase 1 studies. A total of 433 patients (346 from double-blind and 87 from open-label phase 3 study) were exposed to ≥ 12 weeks of treatment and 71 patients completed 26 weeks of treatment. The patient population in the phase 3 study was similar to the target population. Overall, this is an adequate safety database for oxybutynin.

Compared to placebo, OTG treatment was associated with an excess of treatment-emergent adverse events in the placebo-controlled phase 3 study (57% versus 48%). More patients in the OTG group than placebo withdrew due to an adverse event (4.9% versus 3.3%) or experienced a treatment-related adverse event (19% versus 11%). Most of the reported adverse events were known anticholinergic side effects and dermatologic application site reactions. The most common adverse events were dry mouth, urinary tract infection, dizziness, application site pruritus, and fatigue. The most common treatment-related adverse events, or adverse reactions, were dry mouth (OTG: 6.9%, placebo: 2.8%) and application site reactions (OTG: 5.4%, placebo: 1%). Compared to placebo, OTG treatment was not associated with an excess of deaths, non-fatal serious adverse events, neurologic, cardiac, hepatic, hematologic, or renal toxicity. No new or unexpected adverse events or reactions were noted in the phase 3 open-label extension or in the phase 1 studies. During the clinical development of OTG, the following 4 safety issues were specifically addressed:

1. Skin tolerability: Skin tolerability was assessed in the 11 integrated safety studies, including the phase 3 study. Skin tolerability was systematically assessed by visually inspecting the gel application area for erythema changes at variable time points after study drug application. Overall, the proportion (< 5%) and severity (mild to moderate) of erythema changes in the OTG group were not significantly greater the placebo group. The risk of developing erythema at the application site did not increase significantly with longer duration of OTG use. Although there is no direct comparison between OTG and Oxytrol TDS, available clinical evidence suggests that skin tolerability of OTG may be better than Oxytrol TDS.

   During the entire phase 3 study (double-blind and open-label), application site adverse reactions were reported by approximately 6% of patients on active treatment compared to 1% of placebo patients. Approximately 2% of OTG-exposed patients discontinued therapy because of application site reactions compared to < 1% of patients on placebo. The incidences of application skin reactions and treatment discontinuation due to an application site reaction increased slightly with longer duration of OTG use.

2. Dermatologic safety: The potential of OTG for skin irritation and skin sensitization was evaluated in 2 placebo-controlled dermatoxicity studies. Results from a 21-day cumulative skin irritation study indicated that OTG is not an experimental skin irritant. In the skin sensitization study, one subject (0.5%) experienced mild contact sensitization to OTG.

3. Person-to-person transference: In a PK transference study, direct physical contact at the OTG application site leads to dermal transfer and systemic absorption of oxybutynin to the untreated

partner. This skin-to-skin transference, however, can be significantly mitigated by covering the application site with clothing.

4. Co-administration of OTG with sunscreen: The absorption and metabolism of oxybutynin were not affected by the application of sunscreen 30 minutes before or after OTG gel application.

Overall, the safety findings of OTG were expected of an oxybutynin product. Although data directly comparing the skin safety of Oxytrol TDS and OTG were not submitted with this application, data available for these 2 products suggest improved skin tolerability with OTG compared to Oxytrol TDS.

1.3.4 Dosing Regimen and Administration

The 1 g 10% OTG dose was selected based on results from studies OG04007 and OG06005. Pharmacokinetic modeling of single doses of 1 g and 3 g 10% OTG predicted that the 1 g dose would most closely match the delivery of Oxytrol TDS (3.9 mg/day). This prediction was confirmed by a direct steady state PK comparison of the 2 products where 1 g 10% OTG produced oxybutynin exposure and plasma drug concentrations similar to those of Oxytrol TDS.

***Reviewer's comment**: The dose selection was based on PK results and not clinical efficacy findings. At steady state, DEO concentration and exposure (Cavg, AUC) was approximately 25% less after OTG dosing than Oxytrol dosing. Although DEO is a pharmacologically active metabolite, the exposure-response relationship of DEO is not well-characterized. According to the clinical pharmacology reviewer, the OXY + DEO concentration and exposure were similar between 1 g 10% OTG and Oxytrol TDS 3.9 mg/day.*

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies or data were submitted for OTG. No formal drug-drug interaction studies have been conducted with Oxytrol TDS. For OTG, the sponsor proposes the same general drug-drug interaction language found in the Oxytrol TDS label, which cautions against the concomitant use of OTG with other anticholinergic products and states the unknown effect of concomitant use of cytochrome P450 enzyme inhibitors.

***Reviewer's comment:** According to the Ditropan label, mean oxybutynin plasma levels increased 3- to 4-fold when Ditropan was administered with a potent CYP3A4 inhibitor (ketoconazole). This drug-drug interaction information, however, cannot be reliably extrapolated to transdermal oxybutynin because the first-pass metabolism of transdermal oxybutynin differs significantly from oral oxybutynin.*

1.3.6 Specific Populations

Gender: Although OTG is indicated for adult patients with overactive bladder, the target population will be primarily older women. The sponsor did not enroll sufficient men to perform a meaningful subset safety analysis based on gender from the controlled safety studies data.

In phase 1 PK studies in healthy volunteers, female volunteers showed slightly greater oxybutynin absorption and metabolism than the male volunteers. The clinical significance of this difference is unknown.

Race: The number of minorities was too small to perform an adequate subset safety analysis based on race from the controlled safety studies data.

Age: In the phase 3 study, approximately 35% of randomized patients were ≥ 65 years old. No overall differences in safety or efficacy were noted between these patients and younger patients.

Renal impairment: OTG has not been evaluated in patients with renal impairment.

Hepatic impairment: OTG has not been evaluated in patients with hepatic impairment.

Pediatric: OTG has not been evaluated in patients < 18 years old. The sponsor requests a waiver for conducting pediatric studies in children from birth through 4 years of age and a deferral of conducting studies in children 5-17 years old until after OTG is approved for use in adults.

Reviewer's comment: *The Pediatric Review Committee (PeRC) granted a pediatric waiver for children ages 0 to 5 years, 11 months, and a pediatric deferral for children ages 6 to 16 years, 11 months. This decision is consistent with previous pediatric waiver and deferrals granted to other anticholinergic products indicated for the treatment of OAB in adults.*

Pregnancy: Oxybutynin is a pregnancy category B based on negative teratogenic findings in preclinical studies. The safety of oxybutynin administration to pregnant women has not been established.

2 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

Oxybutynin Transdermal Gel 10% is a clear, smooth hydroalcoholic gel containing 100 mg oxybutynin chloride per gram of gel. OTG 10% is available in a 1 gram (1.14 mL) unit dose containing 100 mg oxybutynin chloride. Each unit dose is packaged in individual sachets constructed of (b) (4) A topically applied unit dose has a nominal *in vivo* delivery rate of 4 mg oxybutynin per day through intact skin. Oxybutynin is delivered as a racemate of R- and S-isomers. Inactive ingredients in OTG 10% are alcohol, USP; glycerin, USP; hydroxypropyl cellulose, NF; sodium hydroxide, NF; and purified water, USP. The quantitative composition of the drug production is provided below in Table 2.

Table 2: Composition of OTG 10%

Component	% by Weight	mg/g	Function
Oxybutynin chloride, USP	10.0	100	Drug Substance
Purified Water, USP			(b) (4)
Alcohol, USP			
Glycerin, USP			
Sodium Hydroxide, (b) (4) (Sodium Hydroxide, NF and Purified Water, USP)			
Hydroxypropyl Cellulose, NF			

Source: Module 2.3, Drug Product, Description of Composition of Drug Product, Table 2.3.1-2, p. 1

2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATION

Overactive bladder (OAB) is a symptom complex comprising chronic symptoms of frequency and urgency with or without urge urinary incontinence (U-UI). These symptoms must be exhibited in the absence of pathological or metabolic disorders (e.g., urinary tract infection, bladder cancer) that might cause such symptoms. In the U.S., approximately 17% of the general adult population, or 33 million adults, meet the criteria for OAB, with one-third of these patients experiencing urinary urge incontinence.[3] The prevalence of OAB increases with age, and more women than men experience U-UI. Overactive bladder has significant impact on the patient's quality of life, ranging from sleep disturbance to interference with social activities to fall and fracture. The mainstays of OAB therapy include patient education, behavioral modifications (e.g., fluid management, timed voiding, bladder drills, prompted voiding), pelvic-floor physical therapy, anticholinergic medications, and rarely, electrical stimulation therapy and surgery in refractory cases. The management of OAB is usually a step-wise approach. Behavioral therapy, which typically includes a combination of patient education, behavioral modifications and pelvic floor muscle exercises, is often the first-line treatment. These conservative measures have been shown to be effective in controlling OAB symptoms in studies of limited duration. Patient compliance with these conservative measures, however, often declines with time because they require significant time and effort on the part of the patient to remain effective.

If the conservative approach is unsuccessful, antimuscarinic pharmacotherapy is added to the regimen of OAB therapy. These drug therapies include oral (immediate release and extended release) and transdermal formulations (Oxytrol transdermal system [Oxytrol TDS]). The approved oral antimuscarinic medications are oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. A systematic literature review found that, compared to placebo, treatment with these agents resulted in a 40% higher rate of cure or improvement, and an absolute mean improvement of 0.6 in both incontinence episodes and voids per day. The absolute treatment benefit over placebo was small, in part because patients who received placebo also did well. This may be due to concomitant bladder training in some of the studies, or training effects from completion of multiple bladder diaries during the trial.[4] Although there are no head-to-head comparison studies, no compelling evidence exists to indicate that one antimuscarinic agent is superior to another in efficacy.[5]

All oral antimuscarinic agents produce adverse reactions resulting from the pharmacologic blockade of cholinergic receptors throughout the body. Examples include inhibition of muscarinic receptors in the salivary gland (dry mouth), the gut (constipation), ciliary muscle of the lens (blurry vision for near objects), heart (tachycardia), and central nervous system (drowsiness, altered cognitive function). The specific safety profile of each antimuscarinic product depends, in part, on its relative affinity for each muscarinic receptor subtype and its PK profile. Extended-release formulations of oxybutynin (Ditropan XL) and tolterodine (Detrol LA) were developed to achieve more consistently steady plasma concentrations and improve tolerability compared with their immediate-release counterpart. However, anticholinergic side effects continue to be a major cause of patient noncompliance and treatment discontinuation.

A transdermal formulation of oxybutynin (Oxytrol TDS) was developed in an attempt to reduce some of the systemic anticholinergic side effects. Unlike the oral route, transdermal delivery of oxybutynin avoids the extensive first-pass metabolism, which leads to decreased conversion of oxybutynin to N-desethyloxybutynin (DEO), a major pharmacologically active metabolite thought to contribute to the anticholinergic side effects. The continuous delivery of oxybutynin via the transdermal route avoids the peak and trough concentrations seen with oral formulation, which may also contribute to improved tolerability. In controlled clinical trials with Oxytrol TDS, the incidence of dry mouth was comparable to

that of placebo, and the incidence of patients discontinuing treatment due to anticholinergic side effects appeared to be less than that observed in clinical trials with oral oxybutynin. However, application site reactions associated with the transdermal delivery system were frequently reported and were the most common reason for treatment discontinuation.

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES

Oxybutynin is available in immediate release (IR), extended release (ER), and transdermal formulations. A summary of the product information of approved oxybutynin products are presented in Table 3. The approval history of these products follows:

- NDA 17-577 for oxybutynin chloride 5 mg tablets (Ditropan®) was approved in July, 1975. The product was approved for use in both adult and pediatric populations.
- NDA 18-211 for oxybutynin chloride 5 mg/5 mL syrup (Ditropan®) was approved in November, 1979. The product was approved for use in both adult and pediatric populations.
- NDA 20-897 for oxybutynin chloride extended release (Ditropan® XL) 5, 10, and 15 mg extended-release tablets was approved for use in adults in December, 1998. The product was approved for use in the pediatric population (≥ 6 years old) in April, 2003, after the terms of the Written Request were sufficiently fulfilled.
- NDA 21-351 for oxybutynin chloride transdermal system (Oxytrol® TDS) (3.9 mg/day, change patch every 3-4 days) was approved for use in adults in March, 2003.

Table 3: Product Information of Approved Oxybutynin Products

Trade name	**Ditropan®**	**Ditropan® XL**	**Oxytrol®**
Formulation	IR oral tablet and syrup	ER oral tablet	Transdermal patch
Labeled Indication	"Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria)"	Same as Ditropan®	"Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency"
Dose and dosing regimens	Tablet: 5 mg Syrup: 5 mg/5 mL <u>Adults</u>: Start with 2.5 mg bid to tid, increase in increments up to maximum of 20 mg/day in divided doses as needed <u>Pediatric patients</u>: 5 mg bid, up to maximum of 5 mg tid	5 mg, 10 mg, 15 mg <u>Adults</u>: Start with 5 or 10 mg once daily, increase in 5 mg increments as necessary (maximum of 30 mg/day) <u>Pediatric patients</u> (≥ 6 years): 5 mg once daily, increase in 5 mg increments as needed (maximum of 20 mg/day)	3.9 mg/day (39 cm^2 patch) Change one system (3.9 mg/day) every 3 to 4 days
Intended population	Adult and pediatric patients (≥ 6 years) with bladder instability due to detrusor instability or neurogenic bladder	Same as Ditropan®	Adults with OAB

Source: Ditropan®, Ditropan® XL, Oxytrol® product labels

2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS

Labeled safety issues with oxybutynin:

- Use is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients at high risk for these conditions.
- Use with caution in patients with clinically significant bladder outflow obstruction or gastrointestinal obstructive or motility disorders, myasthenia gravis, hepatic or renal impairment, or the frail elderly.
- Use with caution in patients with pre-existing dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms (in oral oxybutynin product label).
- Monitor for central nervous system effects (e.g., hallucinations, agitation, confusion, and somnolence) during first few months of drug use or with dose increase (in oral oxybutynin product label).
- Symptoms of hyperthyroidism, coronary artery heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy may be aggravated.
- Common adverse reactions are those associated with anticholinergic effects (e.g., dry mouth, dizziness, constipation, nausea, blurred vision, heat prostration).

Safety issues related to transdermal formulation:

- Adverse application site reactions include application site pruritus, erythema, macules, rash, and vesicles, with application site pruritus and erythema being the most common. In controlled clinical trials, application site reactions were reported by 16-21% Oxytrol TDS-exposed patients, 5% of whom reported severe reactions. In the same studies, dermatologic reactions led to premature discontinuation in approximately 10% of Oxytrol TDS-exposed patients. Rarely, cases of contact sensitization have been observed in clinical trials with active TDS treatment.
- Person-to-person transference: Direct physical contact at the application site of gel products (e.g., testosterone) can result in systemic drug absorption in untreated partners. The risk of skin-to-skin transference may be significantly reduced by covering the application site with clothing.
- Topical gels containing alcohol are flammable and open flame/smoking should be avoided during the application of these gel products.

2.5 PRESUBMISSION REGULATORY ACTIVITY

The sponsor opened IND 67,126 (oxybutynin transdermal gel 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 OTG, the sponsor planned to conduct one large phase 3 with 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 OTG 10%.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

There are no outstanding issues from other review disciplines and consults.

3.1 CMC and PRODUCT MICROBIOLOGY

Chemistry: Recommends approval of this NDA from a CMC perspective.

On January 23, 2009, the Office of Compliance rendered an "Acceptable" recommendation for the inspection sites. The CMC reviewer concluded the following:

> "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."

Microbiology: Recommends approval from a microbiology perspective.

3.2 ANIMAL PHARMACOLOGY AND TOXICOLOGY

Recommends approval from a pharmacology/toxicology perspective.

3.3 CLINICAL PHARMACOLOGY

Recommends approval from a clinical pharmacology perspective. The clinical pharmacology reviewer concludes that the sponsor has demonstrated that the systemic exposure of oxybutynin from OTG and the currently approved transdermal patch are similar.

3.4 STATISTICS

Recommends approval from a statistical perspective. The statistics reviewer recommends that the p-values for the secondary endpoints not be included in the label because they were not pre-specified and there were no statistical adjustment for testing multiple endpoints.

Reviewer's comment: *During an internal DRUP meeting, the DRUP clinical and statistic review teams agreed that the p-value for the secondary endpoint of urinary frequency may be labeled because of the following reasons: 1) it is a clinically meaningful endpoint for OAB and, 2) the results of the statistical testing of the primary endpoint and the secondary endpoints were robust and persuasive. Because the clinical significance of the secondary endpoint of average urine volume voided was questionable, the teams concluded that the results of this endpoint should be presented in a descriptive manner in the product label.*

During the labeling negotiations teleconference on January 13, 2009, the Division agreed to allow the inclusion of the p-values for the secondary endpoints of urinary frequency and average volume voided,

primarily because statistical significance data for these 2 secondary endpoints were allowed in all other OAB drug labels.

3.5 CONSULTS FROM OTHER DIVISIONS

3.5.1 Division of Scientific Inspection (DSI)

Because there was only one phase 3 study to support the safety and efficacy of OTG, the Division consulted DSI to conduct a routine inspection of 2 large study sites. DSI inspected 2 study sites with large enrollment numbers (Dr. Schmidth-24 subjects; Dr. Deeths-35 subjects) and found no irregularities. DSI concludes that no action is indicated.

3.5.2 Office of Surveillance and Epidemiology (OSE)

- Division of Medication Error Prevention and Analysis (DMEPA): DMEPA accepts the tradename of "Gelnique" and also accepts the revised carton container label, which incorporated all of DMEPA's recommendations.
- Division of Risk Management (DRISK): DRISK's recommendations have been incorporated into the final Patient Labeling agreed upon by the Division and the sponsor.

3.5.3 Study Endpoints and Labeling Development Team (SEALD):

SEALD's recommendations were incorporated into the final product label agreed upon by the Division and the sponsor.

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

DDMAC's recommendations were incorporated into the final product label agreed upon by the Division and the sponsor.

3.5.5 Pediatric Review Committee (PeRC)

- Pediatric waiver (0-4 years): A pediatric waiver was requested and granted for OTG in children ages 0 to 5 years, 11 months.
- Pediatric deferral (5-16 years old): A pediatric deferral was requested and granted for OTG in children ages 6 to 16 years, 11 months. See Section 8.3 (Special Populations-Pediatrics) of this clinical review for further details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

This NDA was submitted entirely in the electronic Common Technical Document (eCTD) format. The following materials were reviewed:

a. Overview section, clinical summaries, and integrated summary of safety
b. Clinical safety and efficacy: Study **OG05009** (" A multi-center, double-blind, placebo-controlled study of the efficacy and safety of daily dosing with Oxybutynin Topical Gel to treat the symptoms of overactive bladder with a 14-week open-label safety extension")
c. Comparative pharmacokinetics: Study **OG04007** ("Single-dose pharmacokinetics of oxybutynin and metabolites following transdermal applications of 3.9 mg/day Oxytrol transdermal system, 3 g of 4.4% topical oxybutynin gel, 1 g of 10% topical oxybutynin gel and 3 g of 10% topical oxybutynin gel to healthy volunteers") and Study **OG06005** ("A steady-state comparison of plasma oxybutynin, N-desethyloxybutynin and R and S enantiomers concentrations following multiple dose application of 1 g oxybutynin topical gel and Oxytrol oxybutynin transdermal system in healthy volunteers")

d. Dermatoxicity: Study **OG05003** (cumulative irritation study) and **OG05004** (skin sensitization study)
e. Other PK studies affecting safety: Study **OG06007** (person-to-person transference) and Study **OG06006** (effect of sunscreen lotion on OTG absorption)
f. 120-Day Safety Update
g. Annual IND reports for IND 67,126, Annual ADE reporting for NDA 21-351 (Oxytrol), Annual NDA report for NDA 21-351

4.2 TABLE OF CLINICAL STUDIES

Table 4 summarizes the clinical studies used to support the safety and efficacy of OTG. All studies, except for OG02020, were conducted in the U.S. under IND 67,126.

Table 4: **Summary of Clinical Studies with OTG**

Type of Study	Objective	Test product	Treatment duration	# of subjects (M/F)
Phase 1				Healthy subjects
OG02020	Bioavailability (BA) and pharmacokinetics (PK)	3 g 4.4% once daily	3 days	12 (10/2)
OG03013	Surface area of application on BA	3 g 4.4% single dose	2 days	22 (11/11)
OG03018	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose, 1 g 13.2% single dose	2 days	22 (10/12)
OG04004	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose 1 g 13.2% single dose	2 days	20 (10/10)
OG04007*	Comparative BA and PK of 3 different OTG formulations and Oxytrol	3 g 4.4% single dose 1 g 10% single dose 3 g 10% single dose 3.9 mg/day Oxytrol single application (one TDS for 3.5 days)	6.5 days	22 (13/9)
OG03005	Steady state BA and PK	3 g 4.4% once daily	8 days	20 (11/9)
OG04008*	Steady state PK and application site bioequivalence	1 g 10% once daily	42 days	40 (20/20)
OG06005*	Steady state PK and comparison with Oxytrol	1 g 10% once daily Oxytrol x 4 applications (each application = 3.5 days)	36 days	22 (12/10)
OG06001*	Effect of sunscreen	1 g 10% single dose	3 days	16 (8/8)

OG06006*	Effect of showering	1 g 10% once daily	35 days	20 (9/11)
OG06007*	Transfer potential	1 g 10% single dose	1 day	52 (25/27)
Dermatoxicity studies				Healthy subjects
OG05003*	Cumulative irritation	1 g 10% once daily 1 g placebo once daily	21 days	45 (14/31)
OG05004	Skin sensitization	0.5 g 10% three times per week for 3 weeks 0.5 g placebo gel 3 times per week for 3 weeks	22 days	225 (87/138)
Phase 3 safety and efficacy				OAB patients
OG05009-double blind*	Safety and efficacy of 1g 10% OTG in target population	1 g 10% once daily 1 g placebo once daily	12 weeks	789 389 OTG (37/352) 400 plac (48/352)
OG05009-open label*	Safety	1 g 10% once daily	14 weeks	216 (22/194)

*Studies using the to-be-marketed dose and formulation (1 g 10% OTG)
Source: Synopses of Individual Studies, Module 2.7.6, Table 2.7.6-1, p. 4-6

4.3 REVIEW STRATEGY

All materials submitted in the NDA were considered during the conduct of this clinical review. Specific details regarding the approach used to conduct this review are outlined below:

- The clinical efficacy review was based entirely on Study OG05009; the safety review included the integrated Study OG05009, the 10 integrated phase 1 studies, the 2 non-integrated dermatoxicity studies, and the non-integrated person-to-person transference study.
- The focus of the efficacy and safety review was Study OG05009 double-blind period. This was the only adequate and well-controlled clinical study appropriately designed to assess drug effect on safety and efficacy.
- Comparative PK studies (OG04007 and OG06005) were reviewed in detail in the clinical pharmacology section to assess the similarity of PK parameters between 1 g 10% OTG and Oxytrol TDS. Pharmacokinetic data pertinent to proposed labeling from the other phase 1 clinical pharmacology studies were reviewed.
- The 2 dermatoxicity studies (OG05003, OG05004), the person-to-person transference study (OG06007), and the sunscreen study (OG06001) were reviewed in detail, and these reviews are contained in Appendices 10.1.2 to 10.1.5, respectively.
- Independent analyses of datasets of the original efficacy and safety variables were conducted throughout the clinical review to explore certain safety/efficacy issues of interest and to verify the sponsor's findings.

4.4 DATA QUALITY AND INTEGRITY

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."

Central laboratory: In OG05009, laboratory testing for safety parameters was performed by (b) (4) [redacted]. Plasma samples were assayed for concentrations of oxybutynin and DEO according to a validated liquid chromatography/mass spectrometry (LC/MS) method developed and validated by (b) (4) [redacted].

Site Monitoring: Study OG05009 study sites were monitored and audited by (b) (4) [redacted]. Audit certificates indicating GCP compliance were submitted for 7 study sites.

Standard Operating Procedures: The sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice, which include archiving of source data, data validation of CRF data, internal audits, documentation of the qualifications of investigators, and the use of a validated central laboratory.

4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES

According to the sponsor, all clinical studies submitted were conducted in compliance with Good Clinical Practices. In support of this, the sponsor submitted samples of informed consent, documents of IRB approval, and required case report forms.

4.6 FINANCIAL DISCLOSURES

Form FDA 3454 (4/06), dated January 18, 2008, and signed by Kevin Barber, Ph.D., Executive Director, Proprietary Regulatory Affairs, Watson Laboratories, was 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 will be 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 [21 CFR 54.2(a)], proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product [21 CFR 54.2(b)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.2(f)]. 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.

5 CLINICAL PHARMACOLOGY

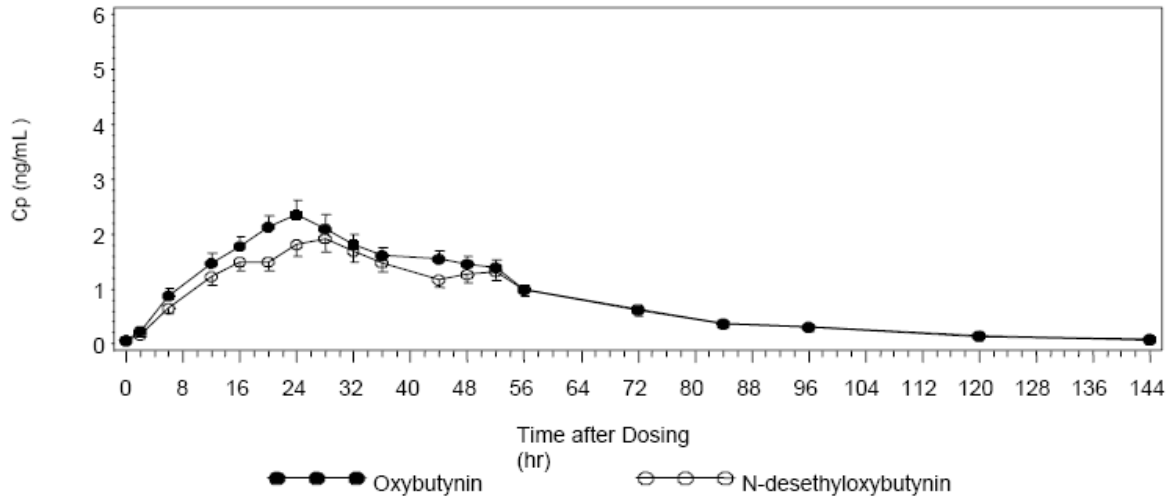
5.1 PHARMACOKINETICS

5.1.1 Drug product pharmacokinetics

Absorption:

Single dose: Transdermal oxybutynin is absorbed through the skin and into systemic circulation by passive diffusion. The estimated nominal dose of oxybutynin absorbed from 1 g 10% OTG is approximately 4 mg, or 4% of the applied dose, based on comparative PK studies with Oxytrol TDS (3.9 mg/day). Plasma oxybutynin profiles after a single-dose of 1 g 10% OTG showed a short lag phase to establish transport through the skin followed by a steady increase in plasma oxybutynin concentrations occurring during the initial 24 hours after drug application, followed by a slow decline in concentrations thereafter. Figure 1 summarizes the pharmacokinetics of oxybutynin and N-desthyloxybutynin (DEO) after a single dose of 1 g 10% OTG.

Figure 1: Mean (± SEM) plasma oxybutynin and N-desethyloxybutynin concentrations following a single 1 gm dose of 10% OTG. (Study OG04007)



Multiple dose: Steady state PK for oxybutynin and DEO following multiple applications (7 days) of 3 g 4.4% OTG was evaluated in study OG03005 following a 7-day washout period after the single dose study. According to the clinical pharmacology reviewer, steady state may have been reached after the second dose. Multiple dose PK was evaluated for the 1 g 10% OTG formulation in study OG04008. Based on racemic oxybutynin and DEO plasma concentrations, oxybutynin absorption was similar when OTG was applied to the abdomen, thighs, or upper arms (see Table 5).

Table 5: Relative Bioavailability of 1 g 10% OTG at Different Application Sites

Variable	Comparison (Test:Reference)	PK Parameter	Ratio	90% Confidence Interval	Bioequivalence Achieved?
Oxybutynin	Thigh: Abdomen	$AUC_{[0-24]}$	1.07	0.93,1.23	YES
		C_{max}	0.99	0.85,1.16	YES
	Arm:Abdomen	$AUC_{[0-24]}$	1.14	0.99,1.31	NO
		C_{max}	1.14	0.97,1.33	NO
DEO	Thigh: Abdomen	$AUC_{[0-24]}$	1.09	0.95,1.26	NO
		C_{max}	1.11	0.96,1.28	NO
	Arm:Abdomen	$AUC_{[0-24]}$	1.09	0.94,1.25	NO
		C_{max}	1.13	0.98,1.30	NO

Source: Study report, Table 11-5, p. 31

***Reviewer's comment**: Using the abdomen as the reference site, bioequivalence of AUC and Cmax for oxybutynin was achieved only between the thigh and abdominal sites, based on 90% confidence intervals. DEO concentrations were not strictly bioequivalent between thigh and abdominal sites or for the upper arm and abdomen for either parameter. Although strict bioequivalence was not achieved based on the 90% confidence intervals, the clinical pharmacology team concluded that the 3 application sites produced similar oxybutynin bioavailability. The magnitude of the differences between the 3 application sites is small compared to the oxybutynin/DEO exposure after oral oxybutynin administration and is not expected to produce clinically important differences in safety and efficacy. Furthermore, patients in the phase 3 study used all 3 application sites on a rotating schedule.*

Metabolism: Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Small amounts of CYP3A4 are found in the skin. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and DEO, which is pharmacologically active. Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism. The AUC ratio of DEO: oxybutynin after multiple doses of 1 g 10% OTG was approximately 1.

Elimination: After multiple applications of 1 g 10% OTG, both oxybutynin and DEO showed biphasic elimination with blood concentrations declining starting at 24 hours post-dose. Elimination was more rapid between 24 and 48 hours after dosing, during which time plasma concentrations of oxybutynin and DEO declined by about 50%. This was followed by a more prolonged terminal elimination phase. The apparent elimination half-lives were 64 hours for oxybutynin and 82 hours for DEO.

Dose-proportionality of pharmacokinetics: No dose proportionality studies with the final OTG formulation were conducted. In a single-dose, 4-way crossover PK study of 1 g 10% OTG and 3 g 10% OTG, AUC and Cmax values more than slightly doubled (less than dose-proportional) when the dose was increased from 1 g to 3 g; the $t_{1/2}$ and t_{max} remained unchanged.

5.1.2 Intrinsic Factors

Gender: In general, female subjects had higher oxybutynin and DEO concentrations (approximately 20-30%) as well as higher DEO:OXY AUC ratios than male subjects. However, these differences are not expected to be clinically significant.

Reviewer's comment: *According to the clinical review of NDA 21-351 (Oxytrol TDS 3.9 mg/day), mean plasma oxybutynin concentrations were generally somewhat higher in males than in females while DEO concentrations were generally higher in females. The clinical implications of these gender differences are unknown but are unlikely to pose any meaningful safety issues.*

Pharmacokinetic studies to evaluate 1 g 10% OTG in the pediatric population or in subjects with renal impairment, liver insufficiency, or other disease states were not performed.

5.1.3 Extrinsic Factors

Showering: Oxybutynin absorption was not affected by showering 1, 2, or 6 hours after application, compared to no shower. Compared to no shower, showering decreased the time to maximum concentration (Tmax) closer to the time of showering (usually within 2 hours of showering), and the change in Tmax is not unlikely to impact safety or efficacy.

Sunscreen: Sunscreen application 30 minutes before or after OTG application did not affect oxybutynin absorption or metabolism.

Person-to-person transference: OTG can be transferred from a treated person to an untreated person via direct skin-to-skin contact at the application site. This dermal transference can be significantly reduced by covering the application site with clothing.

Drug-drug interactions: No studies were performed with OTG.

5.1.4 Population Pharmacokinetics

In the phase 3 study double-blind period, blood samples were obtained from all enrolled patients using sparse collection techniques for analysis of oxybutynin and DEO plasma concentrations. Mean plasma concentrations of oxybutynin and DEO were similar across all study visits. The sponsor concluded that steady state was achieved by Week 1 by performing a paired t-test of the difference in oxybutynin concentrations at Week 1 and Week 4. A summary of plasma concentrations of oxybutynin and DEO for OTG-treated patients is presented in Table 6.

Table 6: Plasma Concentrations (ng/mL) of Oxybutynin and DEO in Phase 3 Study (mITT)

Analyte*	Week 1 N=364	Week 4 N=357	Week 8 N=338	Week 12 N=308	Endpoint (LOCF)
OXY	6.3 (5.6)	6.1 (5.2)	6.1 (5.4)	6.1 (5.9)	6.0 (5.9)
DEO	6.7 (6.3)	6.7 (6.5)	6.8 (7.1)	7.2 (7.8)	7.1 (8.0)
DEO:OXY	1.13 (0.5)	1.16 (0.6)	1.18 (0.7)	1.2 (1.0)	1.2 (1.0)

*Blood concentrations expressed as mean (SD), Source: Study report, Table 14.4-1, p. 3279-80

Plasma concentrations of oxybutynin and DEO were summarized for gender, race (Caucasian versus non-Caucasian), geriatric status (< 65 years old versus ≥ 65 years old), and BMI category (< 32 kg/m^2 versus ≥ 32 kg/m^2). Overall, the following groups had slightly higher oxybutynin concentrations than their comparative counterpart: women, Caucasians, and geriatric patients. No differences were observed between the two BMI categories. See Table 7.

Table 7: Plasma Concentrations (ng/mL) of Oxybutynin and DEO at Endpoint by Subgroups

Analyte*	Geriatric		Gender		Ethnicity	
	< 65 years	≥ 65 years	Males	Females	Caucasian	Non-caucasian
N	243	137	35	345	337	43
OXY	5.5 (6.1)	6.8 (5.4)	3.9 (2.8)	6.2 (6.1)	6.2 (6.0)	3.9 (4.4)
DEO	6.4 (7.8)	8.3 (8.4)	4.2 (3.5)	7.4 (8.3)	7.4 (8.2)	5.1 (6.4)
DEO:OXY	1.2 (0.9)	1.3 (1.1)	1.3 (1.8)	1.2 (0.8)	1.2 (0.9)	1.3 (1.2)

*Blood concentrations expressed as mean (SD)
Source: Study report, Tables 14.4-2 to 14.4-4, p. 3289-3300

Reviewer's comment: *Other than geriatric patients, too few males and non-Caucasians were enrolled to draw meaningful conclusions. Given the extensive inter-subject variability in oxybutynin and DEO exposure, these differences are unlikely to result in clinically significant differences in safety or efficacy.*

5.1.5 Comparative Pharmacokinetics

Study OG04007 (single-dose): This was a single-dose, 4-period, open-label, randomized, crossover investigation comparing the PK of Oxytrol TDS (3.9 mg/day), 3 g 4.4% OTG, 3 g 10% OTG, and 1 g 10% OTG. The sequence of treatment was randomized for each subject, with a 7-day washout period between each treatment. Serial blood sampling was obtained for 144 hours for each treatment period. The abdomen was the only application site used in this study. Results of the study are summarized in Table 8.

Table 8: Mean (SD) PK Values of Summed OXY + DEO Concentrations (N=20)

Parameter (OXY+DEO)	Oxytrol TDS	1 g 10% OTG	3 g 10% OTG	3 g 4.4% OTG
AUC_{0-144} (ng/mL.hr)	614.4 (230.2)	219.5 (78.5)	498.9 (212.4)	325.0 (110.9)
Normalized AUC (ng/mL)*	175.54 (65.8)	219.5 (78.5)	498.9 (212.4)	325.0 (110.9)
Cmax (ng/mL)	8.61 (3.5)	4.67 (1.9)	9.9 (5.6)	6.4 (2.4)
T ½ (h)	18.6 (4.4)	28.4 (11.9)	26.7 (8.5)	26.1 (6.2)
Median Tmax (h)	28.0	24.0	26.0	26.0
DEO:OXY	1.06 (0.4)	0.90 (0.4)	0.85 (0.4)	0.88 (0.3)

*A dose-normalized AUC was calculated for each Oxytrol application that individually divided the Oxytrol AUC (0-144) by 3.5 days to compare to a daily gel application.
Source: Study report, Synopsis and Tables 11-1 to 11-5, p. 2, p. 29-34

Based on a best-fit plasma concentration-time profile modeling using the measured single-dose plasma concentration data to predict plasma concentration profiles for 14 days of dosing, daily doses of 1 g 10% OTG appeared to provide steady state PK characteristics comparable to that of Oxytrol TDS applied every 3-4 days.

Study OG06005 (steady-state): This was an open-label, 2-period, multiple dose, randomized, crossover study evaluating the comparative steady state PK of 1 g 10% OTG and Oxytrol TDS. Subjects were treated with 18 daily doses of 1 g 10% OTG and 5 consecutive applications of Oxytrol TDS (4 applications x 3.5 days per application, followed by one final 4-day application) in a randomized sequence. Blood sampling was for plasma oxybutynin, DEO, and enantiomer concentrations measurements at 0 hours (immediately prior to the gel/TDS application), and at 12, 24, 36, 48, 60, 72, 84 and 96 hours following the final 4-day application of the TDS and final 4 daily applications of OTG. A

minimum 14-day washout separated the two treatment regimens. The sequence of application sites for Oxytrol (abdomen/buttocks/hip) and OTG (abdomen/thigh/upper arm) was randomized for each subject. Results of comparative PK are summarized in Table 9.

Table 9: Summary of Oxybutynin and DEO PK by Treatment

PK Parameter*	Analyte	1 g 10% OTG N=20	3.9 mg/dayTDS N=20
$AUC_{(0-96)}$ (ng.hr/mL)	OXY DEO DEO:OXY	321.7 (112.3) 264.4 (97.0) 0.77 (0.2)	312.5 (67.6) 338.0 (116.9) 1.07 (0.22)
C_{avg} (ng/mL)	OXY DEO	3.35 (1.17) 2.57 (1.01)	3.26 (0.7) 3.52 (1.22)
C_{max} (ng/mL)	OXY DEO	5.99 (2.58) 4.35 (2.3)	4.82 (1.31) 4.98 (1.7)
T_{max} (h)	OXY DEO	36.0 (33.0) 44.4 (32.1)	40.8 (23.5) 35.4 (20.0)

*All values are expressed in mean (SD) values
Source: Study report, Tables 11-3 and 11-4, p. 27-28

The mean (SD) $AUC_{(0-96\ h)}$ ratios of DEO:OXY for OTG was 0.77 (0.2) and 1.07 (0.2) for TDS, indicating that oxybutynin delivered by the gel formulation underwent less metabolism than a patch formulation. Results of concentrations and PK parameters of oxybutynin and DEO enantiomers are summarized in the Tables 10 and 11.

Table 10: Summary of R- and S-Oxybutynin Pharmacokinetics by Treatment

Parameter*	OTG		TDS	
	R-OXY	S-OXY	R-OXY	S-OXY
AUC_{0-96} (ng.h/mL)	143.3 (47.9)	178.3 (65.0)	138.6 (29.7)	173.9 (39.8)
C_{avg} (ng/mL)	1.49 (0.5)	1.86 (0.7)	1.44 (0.3)	1.81 (0.4)
C_{max} (ng/mL)	2.67 (1.1)	3.32 (1.5)	2.11 (0.6)	2.72 (0.7)
C_{min} (ng/mL)	0.81 (0.2)	0.97 (0.23)	0.79 (0.2)	0.98 (0.4)
T_{max} (h)	34.8 (32.1)	36.0 (33.0)	41.4 (23.2)	37.8 (21.8)

*PK parameters are expressed in mean (SD) values
Source: Study report, Table 11-7, p. 31

Reviewer's comment: *At steady state, the oxybutynin concentrations and PK parameters of OTG were similar to those of Oxytrol TDS. For both products, S-OXY concentration and exposure were approximately 25% higher than R-OXY concentrations.*

Table 11: Summary of R- and S-DEO Pharmacokinetics by Treatment

Parameter*	OTG		TDS	
	R-DEO	S-DEO	R-DEO	S-DEO
AUC_{0-96} (ng.h/mL)	143.2 (45.9)	103.2 (57.0)	197.4 (74.7)	140.6 (64.0)
C_{avg} (ng/mL)	1.49 (0.5)	1.07 (0.6)	2.06 (0.8)	1.46 (0.7)
C_{max} (ng/mL)	2.51 (1.2)	1.86 (1.2)	2.96 (1.1)	2.06 (0.9)
C_{min} (ng/mL)	0.86 (0.2)	0.61 (0.3)	1.2 (0.5)	0.9 (0.5)
T_{max} (h)	45.0 (31.4)	51 (30.4)	31.2 (17.2)	33.0 (22.7)

*PK parameters are expressed in mean (SD) values
Source: Study report, Table 11-8, p. 32

The AUC $_{(0\text{-}96)}$ DEO:OXY ratios for R and S isomers indicate slightly greater metabolism following TDS dosing than OTG dosing. The ratios for R-isomer for TDS and OTG were 1.41 and 1.03, respectively. The ratios for S-isomer for TDS and OTG were 0.78 and 0.56, respectively.

Reviewer's comment:

- *At steady state, DEO concentration and exposure (Cavg, AUC) was approximately 25% less after OTG dosing than Oxytrol dosing.*
- *Although DEO is a pharmacologically active metabolite, the implication of these differences on clinical efficacy is unknown, in part, because the exposure-response relationship of DEO is not well-characterized.*
- *According to the clinical pharmacology reviewer, the concentration and exposure of OXY + DEO were similar after Oxytrol TDS and OTG dosing.*

5.3 EXPOSURE-RESPONSE RELATIONSHIP

Exploratory exposure-response analyses were conducted by using linear regression to test whether there was a linear relationship between the changes from baseline in the primary and key secondary efficacy endpoints and plasma concentrations of oxybutynin and DEO. There was no significant correlation between oxybutynin or DEO concentrations and the key efficacy endpoints.

5.4 CLINICAL PHARMACOLOGY CONCLUSIONS

- 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 a 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 those observed in clinical pharmacokinetic studies.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

The sponsor seeks the indication of "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency."

6.1.1 Methods

The primary objective of the efficacy review was to assess whether OTG treatment resulted in clinically and statistically significant improvement in OAB symptoms over placebo. The efficacy assessment was based entirely on the findings of Study OG05009, as this was the only study in the clinical development of OTG that evaluated the clinical outcomes of OTG treatment. The efficacy findings of Study OG05009 were reviewed in detail in this section; independent analyses of the submitted datasets of OG05009 were

conducted to verify the sponsor's efficacy findings; and the treatment effect of OTG was compared to those of other approved OAB products for consistency of performance.

6.1.2 General Discussion of Endpoints

Registration of OAB drug treatment in the U.S. is generally based on the treatment effect on the number of urinary incontinence episodes, urinary frequency, or both.

- Number of incontinence episodes per day: The data for this endpoint is usually captured by patient-reported urinary diary (3-day or 7-day diary). This is an accepted primary clinical endpoint in phase 3 trials for OAB treatment.
- Urinary frequency: Because a significant proportion of OAB patients do not have urinary incontinence and experience only urinary urgency and frequency, urinary frequency is usually a key secondary endpoint or sometimes used as a co-primary endpoint.
- Average urine volume per void: This clinical endpoint provides supportive evidence of an anticholinergic effect on the bladder (increase in bladder capacity) and usually serves as a secondary endpoint.
- Incontinence-specific Quality of Life (QoL) patient-report outcome instruments:
    a. King's Health Questionnaire (KHQ): The KHQ is a condition-specific, 21-item instrument that measures the impact of urinary incontinence on multiple and broad aspects of health-related quality of life. It consists of 7 multi-item domains (role limitations, social limitations, personal relationships, emotions, sleep and energy, and severity [coping] measures). In addition, 2 one-item questions address incontinence impact and general health perception. The instrument also includes the multi-item symptom severity scale that measures the severity of urinary symptoms.

    b. Incontinence Impact Questionnaire (IIQ): The IIQ is a condition-specific, 30-item instrument that measures the impact of urinary incontinence on 4 domains/subscales: physical activity, travel, social/relationships, and emotional health. All questions are scored on a 4-point Likert scale based on the severity of the impact of UI (0="not at all"; 1="slightly"; 2="moderately"; 3="greatly"). For each subscale, the score ranges from 0-100; the total score, which is a summation of the score of each subscale, ranges from 0-400. The higher the score, the more severe of an impact urinary incontinence has on the patient's health-related quality of life.

6.1.3 Study Design

6.1.3.1 Study Objectives

- Primary: To compare the efficacy of 1 g 10% OTG with placebo gel administered once daily during a 12-week treatment period
- Secondary: To compare additional efficacy measures (urinary frequency, urine void volume, nocturia, quality of life [QoL] evaluations), safety assessment of OTG treatment with placebo. In addition, population pharmacokinetics of oxybutynin and N-desethyloxybutynin were evaluated.
- Open-label: To evaluate the dermatologic safety of chronic OTG use

6.1.3.2 Study conduct and procedures

Study OG05009 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy and safety of 1 g 10% OTG in the symptomatic improvement of OAB after 12 weeks of treatment. The final study protocol dated June 28, 2006, consisted of 3 periods: screening, double-blind, and open-label safety extension. The original protocol dated September 8, 2005, consisted of a screening period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period (DB period). In Amendment #1 dated June 28, 2006, a 14-week open-label safety extension period (OL period) for approximately 200 patients from sites with the highest enrollment was added to the protocol of OG05009.

Study OG05009 enrolled adult patients with OAB with symptoms of urinary urge incontinence and urinary frequency not related to chronic illness, anatomical weakness or abnormalities, or medication. The initial 2 weeks of the screening period was a washout period for treated patients or a disease stabilization period for treatment-naïve patients. During these 2 weeks, all patients received bladder and fluid management training. These 2 weeks was followed by a 1-week baseline evaluation to complete the 3-day urinary diary, and an additional 1 week, if necessary, to repeat the 3-day urinary diary. Eligible patients then 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 double-blind (DB) period. Clinic visits were scheduled 1 week after the first study drug dose, then approximately every 4 weeks thereafter (Weeks 1, 4, 8 and 12) (see Appendix 10.1.1 [a] for details of study schedule). The maximum total duration of the screening and DB treatment periods was 16 weeks. Baseline and each follow-up visit included assessment of the following:

- 3-day urinary diary, 2-day voided volume, and QoL questionnaires (King's Health Questionnaire, IIQ). A 3-day urinary diary was recorded during the week immediately prior to the indicated visit beginning at least 4 days prior to the visit. Voided volume of normal voids was recorded on 2 consecutive days of the 3-day diary.
- Vital signs
- Assessment of adverse events, concomitant medications, and skin tolerability
- Sachet counting for compliance assessment

Physical examination, 12-lead ECG, clinical laboratory tests (complete blood count, chemistry, and urinalysis), urine pregnancy test for women of childbearing potential, and post-void residual (PVR) were assessed at baseline and at Week 12/ET visit. Serum Prostate Specific Antigen (PSA) was measured at screening for eligibility purposes.

Pharmacokinetic assessments: Blood was collected for plasma concentration of oxybutynin and DEO during visits occurring at Weeks 1, 4, 8, and 12/ET post-randomization.

Open-label safety extension: All patients enrolled in the open-label (OL) extension period self-administered 1 g 10% OTG daily to rotating sites of the abdomen, upper arms/shoulders, and thighs for 14 weeks. Clinic visits were scheduled for Weeks 19 and 26 post-randomization. During these 2 visits, vital signs, concomitant medications, adverse events, and skin tolerability were assessed. At the Week 26/ET visit, clinical laboratory tests (complete blood count, chemistry, urinalysis, urine pregnancy test for women of childbearing potential) and the QoL questionnaires were also assessed. Urinary diary data were not obtained during the OL period.

The sponsor planned to enroll 700 subjects from 76 study sites for the double-blind period. For the open-label safety extension, the sponsor planned to enroll 200 subjects who completed the double-blind period to ensure that at least 50 subjects received 6 months of active drug.

***Reviewer's comment**: The general study design and procedures are acceptable.*

6.1.3.3 Eligibility Criteria

The study population consisted of patients with a history of urge urinary incontinence and urinary frequency. Urinary symptoms were evaluated during screening through a specific urinary 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, meeting the following criteria as documented by a completed 3-day urinary diary: average of ≥ 8 urinary voids per day, ≥ 4 urge urinary incontinence episodes per 3 days, average urine void volume of ≤ 350 mL per void, and a PVR ≤ 250 mL. Patients were excluded if their OAB symptoms were related to chronic illness, anatomical weakness or abnormalities, or medication use; if they had a history of lower urinary tract surgery within the previous 6 months; a diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome, or one or more treatable conditions that may cause urinary incontinence or urgency (see Appendix 10.1.1 [b] for a comprehensive list of inclusion and exclusion criteria).

***Reviewer's comment**: The eligibility criteria are appropriate for the target population.*

6.1.3.4 Efficacy Endpoints

Primary:

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

Secondary: Change from baseline to Endpoint in the double-blind period in the following:

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

***Reviewer's comment:** The Division currently does not accept the IIQ and KHQ questionnaires as valid PRO instruments to support labeling claims. In the 74-Day letter, the Division notified the sponsor that the IIQ and KHQ are considered exploratory endpoints and that the Division did not anticipate including data from these questionnaires in labeling. All currently approved oxybutynin product labels include efficacy data on the number of incontinence episodes, urinary frequency, and average urinary volume per void, although the most clinically meaningful endpoints are urinary frequency and incontinence episodes. The average volume per void is a pharmacodynamic endpoint.*

6.1.3.5 Data Analysis

Statistical issues are discussed in detail in the Statistical Review by the statistics team. A brief overview of the most important statistical analyses is presented in this section. No interim analyses were planned or conducted.

Sample size: Approximately 700 enrolled subjects (350 per treatment group) would provide for 85% power to detect a difference in the change from baseline urinary incontinence episode between active drug and placebo assuming a between-group treatment difference of -0.52 per day at Week 12 (LOCF) (Active = -2.55, Placebo = -2.03), a common standard deviation of 2.25 episodes per day, using a 2-sided

test at a significance level of 0.05. Estimates of treatment effect and variability were based on the findings of the most recent safety and efficacy study of Oxytrol (OG002005).

The sample size for the open-label phase was designed to ensure that at least 50 subjects receive a total of 6 months of active drug. By enrolling 200 subjects completing the double-blind phase, approximately 100 would have already received active treatment for 3 months.

Analysis Populations: Four patient populations were defined for statistical analysis:

1. *Modified Intent-to-Treat (mITT):* This was the primary efficacy analysis population and 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.
2. *Intent-to-Treat (ITT):* This was a secondary efficacy analysis population and was defined the same as the mITT population, except in the case of misrandomization, the randomized treatment was to be used in the summary statistics and data analysis.
3. *Evaluable:* This was a secondary efficacy analysis population and included all patients in the mITT population who were without major protocol violations, completed the double-blind period, and provided data for the primary efficacy endpoint at Week 12.
4. *Safety:* All subjects who received at least one dose of study drug.

Datasets: The last-observation-carried-forward (LOCF) and observed cases (OC) datasets were used for summary statistics and data analysis, with the LOCF dataset being the primary.

Efficacy Analyses: All statistical testing were conducted at $\alpha = 0.05$ (two-sided) on the null hypothesis of no difference between the treatment groups.

Primary endpoint: The primary efficacy analysis compared the change in number of urinary incontinence episodes per day from baseline to Endpoint (Week 12/LOCF) between OTG and placebo groups. The number of urinary incontinence episodes was obtained from a 3-day urinary diary. The average number of episodes per day was calculated by dividing the total number of incontinence episodes recorded on the 3-day urinary diary by the number of days with data recorded in the diary. The primary efficacy analysis was analyzed for the mITT population with LOCF imputation for missing data. A secondary efficacy analysis was conducted on the ITT population.

Secondary endpoints: Analyses of secondary endpoints compared the change in average daily urinary frequency, nocturia, urine volume per void, IIQ domain scores and total score, and KHQ domain scores from baseline to Endpoint (Week 12 (LOCF) between treatment groups. The analysis of secondary endpoints was performed using the mITT population.

The analyses for the primary and secondary efficacy parameters were also repeated for the Evaluable population.

Pharmacokinetic Analysis:
Plasma concentration data for oxybutynin, DEO, and the ratio of DEO to oxybutynin were summarized by visit for the active treatment group using descriptive statistics for the mITT population. Simple linear regression was used to determine if there was a linear relationship between the change from baseline in urinary incontinence episodes, average daily urinary frequency, and urine volume per void and plasma concentrations; age and plasma concentrations; and weight and plasma concentrations.

***Reviewer's comment**: The Division agreed to the final Statistical Analysis Plan for OG05009 in a letter dated September 20, 2007. There were no changes to the conduct or planned analyses of OG05009.*

6.1.4 Efficacy Findings of Study OG05009

The study was conducted at 76 sites throughout the U.S., with study sites enrolling from 4 to 35 patients. The original protocol was dated September 8, 2005, and one amendment to the protocol was dated June 28, 2006. The final protocol was dated June 28, 2006. The first patient visit occurred on June 12, 2006, and the last patient visit occurred on May 17, 2007. The database was locked on August 23, 2007, and the final study report was dated December 21, 2007.

6.1.4.1 Subject Disposition

Double-blind period: A total 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 patients (11%) discontinued prematurely, primarily due to an adverse event (32 patients [4.1%]), patient's decision to withdraw or inability to participate further (30 patients [3.8%]), and lost to follow-up (17 patients [2.2%]). More OTG-exposed patients discontinued because of an adverse event, whereas more placebo patients discontinued because of patient refusal/inability to participate further. The distribution of other reasons for discontinuation was comparable between the 2 treatment groups. See Table 12.

Table 12: 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

Open-label safety extension: Of the 701 patients who completed the double-blind period, 216 entered the open-label safety extension from 24 selected study sites. Of the 216 patients, 175 (81%) completed the 14-week safety extension. Forty-one patients (19%) discontinued prematurely, primarily due to patient refusal/inability to participate further (23 patients, 10.6%) and an adverse event (15 patients, 6.9%). Table 14 summarizes the disposition of the patients in the safety extension period by randomized treatment group in the double-blind period. At the completion of the open-label extension, patients randomized to placebo in the DB period who entered the safety extension ("Double-Blind Placebo") received a maximum of 14 weeks of active treatment, and those randomized to OTG in the DB period who entered the safety extension (Double-Blind OTG) received a maximum of 26 weeks of active treatment. The subject disposition and the distribution of reasons for premature discontinuation were similar between these 2 groups in the open-label period. See Table 13.

Table 13: Subject Disposition in the Open-Label Safety Extension

	Double-Blind Placebo N=107 n (%)	**Double-Blind OTG** N=109 n (%)	**Overall** N=216 n (%)
Completed	87 (81.3)	88 (80.7)	175 (81)
Discontinued	20 (18.7)	21 (19.2)	41 (21)
Discontinuation due to:			
* Adverse event	8 (7.5)	7 (6.4)	15 (6.9)
* Patient refusal/inability to participate further	11 (10.3)	12 (11.0)	23 (10.6)
* Lost to follow-up	1 (0.9)	0 (0.0)	1 (0.5)
* Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
* Investigator recommendation	0 (0.0)	0 (0.0)	0 (0.0)
* Other	0 (0.0)	2 (1.8)	2 (0.9)

Source: Study Report, Table 10-2, p. 52

6.1.4.2 Misrandomization, Protocol Violations and Compliance

Misrandomization: Nine patients were randomized out of sequence, six of whom received a treatment different from the randomized treatment. Four patients (13218, 14121, 16517, and 17214) received placebo when they should have received active treatment, and two patients (16518 and 17205) received active treatment when they should have received placebo.

Protocol Violations: A total of 47 patients had a total of 47 major protocol violations, all of which occurred during the double-blind period. The most common violations included not withdrawing patients who had withdrawal criteria (25 patients, mostly due to a urinary tract infection) and a significant lack of compliance (14 patients).

***Reviewer's comment**: Overall, 23 placebo patients and 24 OTG patients had a major protocol violation.*

Compliance: Compliance was measured as the ratio of the number of sachets used divided by the number expected to be used. Over the 12-week double-blind period, the mean overall treatment compliance was approximately 90% for each treatment group. During the open-label period, the mean compliance was approximately 89% in each treatment group (double-blind placebo and double-blind OTG). One patient was withdrawn from the study (Patient 12603-OTG) because of significant lack of compliance, and 14 patients were excluded from the Evaluable population due to compliance < 50%.

***Reviewer's comment:** A review of the compliance dataset indicated that, during the double-blind period, 33 patients on active treatment and 29 patients on placebo had at least one visit where compliance rate was < 50%. In the OTG group, there were 47 visits in 33 patients where compliance was < 50%; in the placebo group, there were 50 visits in 29 patients where compliance was < 50%. Overall, the incidence of non-compliance was similar between the 2 treatment arms during the double-blind period and therefore, should not alter efficacy results.*

6.1.4.3 Data Sets Analyzed

Three patient populations were used in the efficacy analysis (mITT, ITT, and Evaluable). Both the mITT and the ITT populations included 789 patients, and the Evaluable population included 663 patients (see Table 14). The ITT population was the same as the mITT population, except data from 9 patients randomized out of sequence were summarized according to the randomized treatment in the former.

Patients excluded from the Evaluable population included the 85 patients (11%) who discontinued before completing 12 weeks of treatment, 33 patients (4%) who had major protocol deviations, and 8 patients (1%) who did not provide data for the primary endpoint at Week 12.

Table 14: Analysis Populations by Treatment

Population	Placebo	OTG	Overall
mITT	400	389	789
ITT	400	389	789
Evaluable	338	325	663

Source: Study report, Table 11-1, p. 54

6.1.4.4 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the 2 treatment groups in the double-blind period of Study OG05009 are summarized in Table 15. The majority of patients were non-Hispanic (94-95%), White (84-89%) females (88-91%). The mean age for both treatment groups was 59 years. Approximately 35% of patients in each treatment group were ≥ 65 years old. Mean duration of incontinence at study entry was 97.4 months (8.1 years) and 107 months (8.9 years) for the placebo and OTG groups, respectively. The median duration of incontinence was 60.0 months (5 years) for both groups. Approximately 27% of placebo patients and 23% of OTG patients have previously or currently been treated with pharmacologic treatment for OAB. Approximately 2% of patients in each treatment group had neurogenic causes of urinary incontinence.

Table 15: 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	n (%)	25 (6.3)	18 (4.6)
* Non-Hispanic	n (%)	375 (93.8)	371 (95.4)
Race			
* White	n (%)	335 (83.8)	346 (88.9)
* Black	n (%)	54 (13.5)	33 (8.5)
* Asian	n (%)	7 (1.8)	6 (1.5)
* Others	n (%)	4 (1)	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

The demographics and baseline characteristics of patients enrolled in the open-label period were similar to those of the double-blind period. 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 with a mean BMI of 31 kg/m^2 and a mean duration of incontinence of 107 months. Approximately 27% of patients have had previous medical treatment for OAB.

Reviewer's comment: *No significant differences in patient characteristics were noted between placebo and OTG-exposed patients or between patients enrolled in the double-blind and those participating in the open-label periods.*

To assess whether patients who withdrew prematurely ("non-completers") differed from those who completed the study ("completers"), this reviewer independently analyzed some key baseline characteristics that could impact study results (Table 16). Compared to the "completers," a slightly greater proportion of non-completers were males, and non-completers also had slightly higher mean number of daily incontinence episodes per day. This reviewer does not anticipate that these differences would bias study results one way or another.

Table 16: Baseline Characteristics of Completers versus Non-Completers (MO's Analysis)

Baseline characteristics	Completers N=701	Non-completers N=88
Age mean (SD) (years)	59.5 (11.9)	58.5 (15.5)
Geriatric status (≥ 65 years old) (%)	36%	36%
Males (%)	10%	15%
# daily incontinence episodes mean (SD)	5.3 (3.1)	5.9 (4.4)

6.1.4.5 Efficacy Results

Primary endpoint: *Change from baseline to Endpoint (Week 12, LOCF) in the number of urinary incontinence episodes per day*

The primary comparison of interest was OTG treatment compared to placebo for the change from baseline to Endpoint in number of urinary incontinence episodes per day. The mean (5.4) and median (4.7) number of daily incontinence episodes at baseline was identical for the 2 treatment groups. At Endpoint, the mean change from baseline incontinence episodes per day was -3.0 for the OTG group (56% improvement) and -2.5 for the placebo group (46% improvement). The mean difference between the active and placebo groups were -0.51 incontinence episodes per day (95% CI: -0.14, -0.87) and this difference was statistically significant ($p < 0.0001$). The median change from baseline in the primary endpoint was -2.7 for the OTG group and -2.0 for the placebo group. Similar results were obtained using the OC dataset. See Table 17.

Table 17: 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,-0.87)** **<0.0001***
		Placebo N=358	OTG N=348
Change from baseline to Endpoint (OC)	Mean (SD) Median p-value	-2.6 (3.1) -2.3	-3.0 (2.8) -2.7 0.0004

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

Reviewer's comment: *There was a wide variability in the number of daily urinary incontinence episodes at baseline and in the changes from baseline, as seen in other OAB phase 3 clinical trials.*

The sponsor used the ITT population in the secondary analysis of the primary endpoint. The results were similar to those obtained with the mITT population (Table 18).

Table 18: Urinary Incontinence Episodes per Day (ITT)

	Statistic	**Placebo N = 398**	**OTG N = 391**
Baseline	Mean (SD) Median	5.3 (3.3) 4.7	5.4 (3.3) 4.7
Change from baseline to Endpoint (LOCF)	Mean (SD) Median p-value	-2.4 (3.0) -2.0	-3.0 (2.8) -2.7 <0.0001*
		Placebo N=356	OTG N=350
Change from baseline to Endpoint (OC)	Mean (SD) Median p-value	-2.6 (3.0) -2.3	-3.0 (2.8) -2.7 0.0003

*Versus placebo comparing least squares adjusted means
Source: Study report, Tables 14.2.1-3, 4, p. 181-2

Reviewer's comment*: Ideally, the ITT population should have been the primary analysis population. However, the efficacy results using the mITT and ITT populations were almost identical. Overall, the efficacy results are consistently positive using different analysis populations and datasets. The efficacy analysis of the primary endpoint using the Evaluable population produced results similar to those obtained with the mITT and ITT populations.*

Reviewer's comment: *The treatment effect of OTG 10% is modest (mean treatment difference -0.5 episode/day) but it is comparable to those observed with other approved OAB products, including Oxytrol TDS. See Table 19. The placebo response was significant in OG05009 (46% improvement from baseline), as seen in other clinical OAB trials. Control arms in randomized trials of urinary incontinence treatment demonstrate variable but real placebo responses, with rates ranging from 30-40% or higher.*[4]

Table 19: Treatment Effect of Other OAB Products

Products	Placebo	Drug	Treatment Effect
Oxytrol TDS (oxybutynin) Trial 1: # incontinence episodes per day Mean (SD) Baseline Mean (SD) change from baseline Trial 2: # incontinence episodes per week Mean (SD) Baseline Mean (SD) change from baseline	 5.0 (3.2) -2.1 (3.0) 37.7 (24.0) -19.2 (21.4)	 4.7 (2.9) -2.9 (3.0) 34.3 (18.2) -21.0 (17.1)	 ***Mean: -0.8 episode/ day*** ***Mean: -1.8 episodes/week***
Detrol LA (tolterodine) # incontinence episodes per week Mean Baseline Mean change from baseline	 23.3 -6.9	 22.1 -11.8	 ***Mean: -4.8 episodes/week or -0.69 episode/day***
Enablex (darifenacin) 7.5 mg* # incontinence episodes per week Median Baseline Median change from baseline	 16 -6 to -9	 16 -8 to -9	 ***Median: -1.5 to -2.8 episodes/week***

*Lowest effective dose
Source: Oxytrol TDS, Detrol LA, Enablex product labels

Compared to placebo, the improvement (decrease) in urinary incontinence episodes with OTG treatment was statistically significant beginning at the Week 4 visit and was maintained throughout the double-blind period (see Table 20).

Table 20: Change from Baseline in Daily Urinary Incontinence Episodes by Visit (mITT, OC)

Weeks post-randomization	Statistic	Placebo	OTG
1	Mean (SD)	-1.8 (2.6)	-2.0 (2.4)
	p-value		0.18*
	n	390	384
4	Mean (SD)	-2.3 (2.9)	-2.7 (2.6)
	p-value		0.0004*
	n	374	366
8	Mean (SD)	-2.5 (2.9)	-3.0 (2.6)
	p-value		0.0002*
	n	359	354
12	Mean (SD)	-2.6 (3.1)	-3.0 (2.8)
	p-value		0.0004*
	n	358	348

*Versus placebo comparing least squares adjusted means
Source: Study report, Table 14-2.1-2, p. 178

The sponsor analyzed the results of an exploratory endpoint: "complete continence" during the double-blind period. This endpoint was defined as the absence of any incontinence episode in a 3-day urinary diary. At Endpoint (LOCF), 69 placebo patients (17.3%) and 108 OTG patients (27.8%) achieved "complete continence." Furthermore, 96 placebo patients (24.0%) and 135 OTG patients (34.7%) achieved "complete continence" at any visit during the double-blind period. Similar results were obtained using the ITT population. See Table 21.

Table 21: Number and Percentage of Patients Achieving Continence (mITT)

Weeks Post-randomization	# patients evaluated Placebo/OTG	Placebo n (%)	OTG n (%)
1 (OC)	390/384	16 (4.1)	25 (6.5)
4 (OC)	374/366	44 (11.8)	74 (20.2)
8 (OC)	359/354	51 (14.2)	89 (25.1)
12 (OC)	358/348	66 (18.4)	103 (29.6)
Endpoint (LOCF)	400/389	69 (17.3)	108 (27.8)
At any visit	400/389	96 (24.0)	135 (34.7)

Source: Study report, Table 14.2.5-1, p. 329

***Reviewer's comment**: In the double-blind, placebo-controlled, active controlled phase 3 trial of Oxytrol TDS (3.9 mg/day), 30% and 22% patients receiving Oxytrol and placebo, respectively, achieved continence. These results are similar to those of OG05009.*

***Reviewer's comment**: "Complete continence" defined by the sponsor meant no urinary incontinence in the 3-day period that the patients were recording the urinary diary data, and not a cure of urinary incontinence. The proportion of patients experiencing "complete continence" at any visit was impressive, both for placebo (1/4) and active treatment (1/3), given the severity of the patients' baseline*

urinary incontinence. The treatment effect of OTG on this endpoint was approximately 10%, which is modest. It is unclear if these extreme "responders" skewed the results for the primary efficacy endpoint.

This reviewer analyzed urinary diary dataset (AF-DIARY.XPT) to further explore details of the complete continence data:

- *There appeared to be a modest treatment effect based on the number of urinary diary entries that were reported as "complete continence." Out of a total of 4511 diary entries, 645 (or 14%) were recorded as "complete continence." In the OTG group, 399 of 2230 entries (or 18%) were reported as "complete continence" compared to 246 of 2281 (or 11%) in the placebo group.*
- *Patients who reported "complete continence" were not clustered at any group of study sites. Sixty-six (66) out of 76 sites had at least one record of "complete continence" entry. Twenty-eight sites had ≥ 10 entries of "complete continence." These 28 sites had 70% of the "complete continence" entries (450 of 645 entries). The following 5 sites had ≥ 20 entries of "complete continence": 135 (34 entries), 155 (31 entries), 128 (27 entries), 166 (22 entries), and 130 (21 entries).*
- *It appears that the patients who had at least one diary entry of "complete continence" had less severe urinary incontinence at baseline compared to those who did not (mean [SD] number of baseline incontinence episodes of 3.8 [2.5] versus 5.6 [3.2]).*

Secondary Endpoints:

a. *Change from baseline to Endpoint (Week 12, LOCF) in daily urinary frequency*

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). The median number of daily urinary frequency decreased by 2.7 in the OTG group compared to the median decrease of 1.7 in the placebo group. See Table 22. Compared to placebo, the improvement (decrease) in daily urinary frequency with OTG treatment was statistically significant beginning at the Week 4 visit and was maintained throughout the double-blind period. Similar results were obtained using the ITT and Evaluable analysis populations.

Table 22: 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

***Reviewer's comment**: Treatment benefit on urinary frequency is clinically important as approximately 2/3 of OAB patients do not have urinary incontinence but only have excessive urinary frequency (and urgency). The mean treatment effect of OTG on urinary frequency (decrease of 0.5 micturition per day) is modest, although it is similar to that observed with Oxytrol TDS. For example, compared to placebo, the mean improvement in urinary frequency with Oxytrol TDS treatment was a decrease of 0.5 to 0.6 micturitions per day and the median improvement was a decrease of 1.0 micturition per day.*

b. *Change from baseline to Endpoint (Week 12, LOCF) in average volume voided per micturition*

The mean (approximately 165 mL) and median (160 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 +17 mL and this difference was statistically significant (p = 0.0018). The median change from baseline in the same efficacy parameter was 0.0 mL for placebo and +11.5 mL for OTG. See Table 23. Compared to placebo, a statistically significant improvement in the average volume voided per micturition with OTG treatment was noted beginning at Week 1 and was maintained throughout the double-blind period. Similar results were obtained using the ITT and Evaluable analysis populations.

Table 23: Average Volume Voided per Void (mITT, LOCF)

	Statistic	**Placebo N = 400**	**OTG N = 389**
Baseline	Mean (SD) Median	167.9 (68.4) 160.6	163.4 (65.9) 160.1
Change from baseline to Endpoint	**Mean (SD)** Median p-value	**3.8 (53.8)** 0.0	**21.0 (65.3)** 11.5 **0.0018***

*Versus placebo comparing least squares adjusted means
Source: Study report, Table 11-8, p. 63

***Reviewer's comment**: Treatment effect on the average volume voided per micturition is a commonly used pharmacodynamic endpoint to assess the anticholinergic effect on bladder storage capacity. It is unlikely, however, that a mean increase of 17 mL in bladder storage is clinically meaningful to an OAB patient.*

The treatment effect of OTG 10% on the average voided volume per micturition is similar to that of Oxytrol TDS. Compared to placebo, the mean increase in the average volume per void with Oxytrol TDS (3.9 mg/day) treatment was approximately +20 mL.

c. *Change from baseline to Endpoint in daily nocturia events*

There were no differences between placebo and OTG treatment in the number of nocturia events at baseline (mean [SD] of 2.5 [1.7]) or at Endpoint (mean [SD] of 1.7 [1.5]).

d. *Change from baseline to Endpoint in the Quality of Life instruments*

Incontinence Impact Questionnaire (IIQ)
During the double-blind treatment period, OTG treatment demonstrated a statistically significant improvement (p = 0.0005) in the IIQ total score when compare to placebo. At baseline, the mean IIQ total score for the mITT OTG group was 183.8, which was slightly higher than that of placebo (170.0). At Endpoint, the mean change from baseline for the OTG group was -72.1 (SD 80.0) or a 39% improvement; the mean change from baseline for placebo was -49.5 (SD 76.6) or a 29% improvement. Consistent and statistically significant improvements were also observed in all subscales at Endpoint. See Table 24.

Table 24: Baseline and Change from Baseline to Endpoint in IIQ (mITT)

IIQ	Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
IIQ Total Score			
* Placebo+	170.0 (88.6)	-49.5 (77.0)	
* OTG+	183.8 (93.9)	-72.1 (80.0)	0.0005
IIQ Subscales			
Travel			
* Placebo	51.4 (27.1)	-15.1 (24.8)	
* OTG	54.9 (27.7)	-20.9 (25.6)	0.0068
Physical Activity			
* Placebo	41.9 (24.0)	-13.0 (21.7)	
* OTG	44.8 (25.1)	-18.0 (23.2)	0.0078
Social Relationships			
* Placebo	32.9 (23.5)	-9.7 (19.3)	
* OTG	37.3 (25.5)	-15.2 (20.1)	0.0019
Emotional Health			
* Placebo	43.9 (24.1)	-11.8 (20.1)	
* OTG	46.9 (25.4)	-18.1 (22.0)	0.0002

+ Placebo N=400; OTG N=389
Source: Study report, Table 11-10, p. 65

King's Health Questionnaire (KHQ)

During the double-blind treatment period, OTG treatment demonstrated a statistically significant improvement ($p \leq 0.05$) in the domains of Incontinence Impact, Symptom Severity, Role Limitations, Personal Relationships, Sleep and Energy, and Severity (Coping) Measures of the KHQ compared to placebo. OTG treatment did not demonstrate statistically significant improvement from baseline to Endpoint in the domains of General Health Perceptions, Physical Limitations, Social Limitations, or Emotions compared to placebo. See Table 25.

Table 25: Baseline and Change from Baseline to Endpoint in KHQ (mITT)

KHQ Domains	Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
Incontinence Impact			
* Placebo+	78.3 (23.7)	-21.3 (27.1)	
* OTG+	79.9 (23.2)	-27.9 (30.0)	0.0023
Symptom Severity			
* Placebo+	18.2 (18.2)	-15.8 (21.8)	
* OTG+	18.6 (18.4)	-20.6 (22.9)	0.0024
Role Limitations			
* Placebo	56.1 (28.3)	-21.3 (27.2)	
* OTG	59.1 (28.4)	-27.1 (29.2)	0.01
Personal Relationships			
* Placebo	21.0 (27.5)	-6.2 (20.0)	
* OTG	25.3 (31.1)	-11.2 (25.0)	0.05
Sleep and Energy			
* Placebo	57.0 (26.0)	-10.3 (22.4)	
* OTG	60.0 (26)	-15.6 (24.2)	0.006
Severity (Coping) Measures			
* Placebo	58.7 (24.6)	-11.1 (19.2)	
* OTG	60.3 (23.9)	-15.3 (21.4)	0.006
General Health Perception			
* Placebo	21.3 (16.8)	0.1 (11.9)	
* OTG	21.4 (17.3)	0.4 (12.2)	0.65
Physical Limitations			
* Placebo	54.8 (29.9)	-16.8 (28.1)	
* OTG	55.7 (29.7)	-20.2 (30.0)	0.11
Social Limitations			
* Placebo	29.6 (26.5)	-10.3 (23.5)	
* OTG	29.9 (28.0)	-11.5 (24.4)	0.45
Emotions			
* Placebo	35.1 (27.6)	-8.4 (24.9)	
* OTG	36.1 (27.1)	-11.7 (24.6)	0.06

+ Placebo N=400; OTG N=389
Source: Study report, Table 11-10, p. 65

***Reviewer's comment**: The IIQ and KQH are considered exploratory endpoints and would not support labeling claims. The sponsor submitted published literature references to support the use of these 2 instruments in measuring treatment benefits in the target population. A review of the submitted literature revealed several key deficiencies of these 2 instruments that may render them inadequate measurement tools for clinical efficacy in OAB registration trials. A few examples of these deficiencies follow:*

IIQ:

- *Study population: The instrument was developed in a focus group consisting primarily of women with genuine stress incontinence who were recruited from a single region in the U.S (Southeast). This patient population may not be generalizable to the study population of OG05009 who primarily experienced urinary urge incontinence.*

- *Item generation and development: There is no evidence of cognitive debriefing to ensure that the instrument is understandable and relevant to the target population.*
- *Psychometric validation: There is no evaluation of test-retest validity. The results of construct validity are marginal given the minimal to modest correlation between the IIQ and other comparators (other PRO's, number of urinary incontinence episodes).*

KHQ:

- *Study population: Unclear if the population in which the instrument was developed for is sufficiently similar to the study population of OG05009.*
- *Psychometric properties: The instrument had domains that did not appear to be relevant to the OAB population (e.g., personal relationship domain, social limitation domain), the instrument items had floor and ceiling effects, and the various domains correlated minimally with other PRO's and clinical endpoints (e.g., number of urinary incontinence episodes).*

The changes in total/domain scores that represent a meaningful clinical treatment are unknown for both of these PRO instruments. Statistical significance is not sufficient to demonstrate a meaningful clinical benefit. Furthermore, simultaneous statistical testing of multiple domains and total scores without adjusting for multiplicity can lead to false positive conclusions.

6.1.6 Efficacy Conclusions

1. The results of the primary 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. The improvement in the urinary incontinence episodes per day is modest but similar to other approved OAB products. The improvements in the key secondary endpoints are modest but consistent with the finding of the primary endpoint.
2. Compared to placebo, OTG treatment resulted in improvement in the primary endpoint from Week 4 to Week 12.
3. The improvement in efficacy parameters was consistent when analyzed by different analysis populations and datasets.
4. The results of the IIQ and KHQ are considered exploratory and will not support labeling claims.

7 INTEGRATED REVIEW OF SAFETY

7.1 METHODS AND FINDINGS

Methods

The following sources were reviewed for safety assessment:

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 adequate and well-controlled 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. Detailed reviews of these studies are presented in Appendix 10.1.2-10.1.4.
3. Annual reports of Oxytrol TDS and IND 67,126 and the 120-day Safety Update.

4. Published literature and approved OAB product labels

***Reviewer's comment**: For clarification purposes, "integrated" studies were those that were included in the Integrated Summary of Safety (ISS) and "non-integrated" studies were those that were not included in the ISS.*

Extent of Exposure
In total, the NDA 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), 216 healthy subjects in the integrated phase 1 studies, and 296 healthy subjects in the non-integrated phase 1 studies.

Integrated Phase 3 study: Overall, 496 patients (389 randomized to active OTG in the double-blind [DB] period + 107 randomized to placebo in the DB period and who received active OTG during the open-label [OL] 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; 85 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 active OTG group. In the open-label period, the mean exposure to active OTG was 89.9 days (range 1-142 days).

There were no significant differences in exposure with regards to gender, race, or geriatric status in the phase 3 study.

***Reviewer's comment**: In the phase 3 study, exposures are categorized by treatment duration of **<12 weeks** and **≥12 weeks**. The **≥ 12 weeks** group include only patients who were randomized to active OTG treatment in the double-blind period and who also entered the open-label period (N=109). The **<12 weeks** group includes patients who received active treatment in the double-blind and did not participate in the open-label study and patients who randomized to placebo in the double-blind period and enrolled in the 14-week open-label extension (even though these patients may have received 14 weeks of active OTG treatment in the open-label extension).*

If one were to evaluate exposure based on the actual duration of treatment (and not by the sponsor's method of < 12 weeks and ≥ 12 weeks described in the paragraph above), then 431 of the 496 patients exposed to at least one dose of 1 g 10% OTG received at least 12 weeks of treatment.

Integrated Phase 1 studies: In the integrated phase 1 studies, 118 subjects were exposed to 1 g 10% OTG, 116 subjects to 3 g 4.4% OTG, 41 subjects to 1 g 13.2% OTG, and 21 subjects to 3 g 10% OTG. Exposure in these studies ranged from 1 to 42 days.

Non-integrated studies: In the cumulative irritation study (OG05003), 45 healthy subjects received daily applications of 1 g 10% OTG for 21 days. In the skin sensitization study (OG05004), 225 healthy subjects received 0.5 g 10% OTG three times a week for 3 weeks followed by a single 24-hour challenge application. In the transference study (OG06007), 26 healthy subjects received one dose of 1g 10% OTG.

***Reviewer's comment**:*
1. *It appears that 1008 subjects (496 OAB patients in the phase 3 study + 216 healthy subjects in the 10 integrated phase 1 studies + 296 healthy subjects in the 3 non-integrated studies), and not 1033 as stated by the sponsor, were exposed to active OTG. The 1033 number may have included the 26*

untreated partners in the transference study (OG06007) who could be exposed to OTG via skin transfer from their treated partners.

2. *In total, 614 subjects were exposed to at least one dose of the to-be-marketed dose/formulation 1 g 10% OTG, and 85 patients were exposed to 6 months of active treatment. Although these exposure numbers are less than those recommended by the ICH guidelines for a chronically administered drug, the safety profile of systemic oxybutynin is well-known. The sponsor fulfilled the Division's request that at least 50 patients receive 6 months of OTG, and the safety exposure of OTG is adequate to evaluate skin safety.*
3. *One hundred seventy-eight (178) subjects were exposed to doses higher than the to-be-marketed dose (100 mg oxybutynin), although 80% of these subjects were exposed only to single doses.*
4. *Although safety data from 10 phase 1 studies and 1 phase 3 study were summarized in the Integrated Summary of Safety (ISS), the sponsor presented the data of the integrated phase 1 studies separately from those of the phase 3 study. This approach is acceptable because the study methodology and patient population differed significantly between the phase 1 and phase 3 studies.*
5. *Overall, the quantity and duration of patient exposure was adequate for an oxybutynin product.*

Protocol defined safety assessments

Key safety assessments included treatment-emergent adverse events, skin tolerability, laboratory tests, physical examination, vital signs, and electrocardiograms. Post-void residual urine volume was measured only in the double-blind period of Study OG05009. Skin tolerability to OTG was assessed in all 11 integrated studies by visual inspection of the application area at various time points post-application. Hematology, serum chemistry, and urinalysis were performed at baseline and at study exit only in the phase 3 study (OG05009). No clinical laboratory test results were summarized for healthy volunteer subjects because laboratory assessments were performed only at baseline for eligibility purposes.

Demographics and baseline characteristics

The sponsor did not pool the demographic and other baseline characteristics of the subjects in the 11 integrated safety studies. Instead, the sponsor presented the demographic and baseline characteristics for 3 different populations from the 11 integrated safety studies as follows: 1) Healthy Volunteers, 2) Controlled Study in OAB Patients, and 3) Controlled and Uncontrolled Study in OAB Patients. The data for the 3 different populations were also presented according to the total daily dose and formulation.

In Study OG05009, the 2 treatment groups were similar with respect to age (mean 59 years), geriatric status (35-37% were ≥ 65 years of age), race (84-90% White), BMI (mean 31 kg/m^2), and gender distribution (88-90% female). The baseline characteristics of patients who received active treatment for < 12 weeks were similar to those who received ≥ 12 weeks of treatment. Subjects in the integrated phase 1 studies consisted of an approximately equal number of healthy male and females, most of whom were White (90%), with an average age of 26 years (none were ≥ 65 years old), and a mean BMI of 24 kg/m^2. All 322 subjects enrolled in the non-integrated studies were healthy subjects, between the ages of 18 and 65 years, and 61% were females.

Summary of overall safety findings of the ISS

An overview of the incidences of adverse events and adverse reactions (drug-related AE's) are presented for the double-blind period of the phase 3 study, open-label period of the phase 3 study, for duration of active OTG treatment, and for the integrated phase 1 studies in Tables 26, 27, 28 and 29, respectively.

Table 26: Summary of AE's in the Double-Blind Phase 3 Study

Assessment	OTG N=389 n (%)	Placebo N=400 n (%)
Any adverse event Drug-related Severe	221 (57) 73 (19) 16 (4)	193 (48) 45 (11) 16 (4)
Serious AE (no deaths)	7 (1.8)	10 (2.5)
Discontinuation Drug-related	19 (4.9) 7 (1.8)	13 (3.3) 7 (1.8)
Application site reactions Leading to discontinuation	21 (5.4) 3 (0.8)	4 (1) 1 (0.3)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 13, p. 28

Reviewer's comment: *Over a 12-week treatment period, the incidences of treatment-emergent AE's and AR's were higher in the OTG group than in the placebo group. Although more discontinuations due to an adverse event occurred in the OTG group, the incidence of discontinuation due to an adverse reaction was similar between the OTG and placebo groups. More patients on placebo than on active treatment experienced a serious adverse event (SAE), although none of the SAE's was considered treatment-related.*

Table 27: Summary of AE's in the Open-Label Phase 3 Study

Assessment	OTG N=216 n (%)
Any adverse event Drug-related Severe	97 (45) 22 (10) 9 (4.2)
Serious AE	0
Discontinuation Drug-related	15 (6.9) 11 (5.1)
Application site reactions Leading to discontinuation	13 (6.0) 9 (4.2)

Source: Study report, Table 12-3, p. 79

Table 28: Summary of AE's in Phase 3 Study by Duration of Active OTG Treatment

Assessment	OTG < 12 weeks* N=387 Mean exposure = 82.0 days n (%)	OTG ≥ 12 weeks** N=109 Mean exposure = 177.3 days n (%)
Any adverse event Drug-related Severe	218 (56) 69 (18) 18 (5)	70 (64) 22 (20) 6 (6)
Serious AE (no deaths)	6 (1.6)	1 (0.9)
Discontinuation Drug-related	27 (7) 13 (3.4)	7 (6.4) 5 (4.6)
Application site reactions Leading to discontinuation	24 (6.2) 8 (2.1)	9 (8.3) 4 (3.7)

*<12 weeks=patients randomized to OTG in DB period but did not enter OL period & patients randomized to placebo in DB period and entered the OL period
**≥12 weeks=patients randomized to OTG in DB period and entered the OL period
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 14, p. 29

Reviewer's comment: *The incidences of application site reactions and discontinuation due to application site reactions were higher in patients treated ≥ 12 weeks (8.3%) than those treated < 12 weeks (6.2%) with OTG.*

Table 29: Summary of AE's in Integrated Phase 1 Studies

Assessment	1 g 10% OTG[1] N=118 n (%)	3 g 10% OTG[1] N=21 n (%)	Other OTG**[1] N=116 n (%)	Oxytrol [1] N=43 n (%)
Any adverse event Drug-related Severe	36 (31) 29 (25) 0	2 (10) 2 (10) 0	38 (33) 27 (23) 0	15 (35) 15 (35) 0
Application site reactions Leading to discontinuation	2 (1.7) 0	0 0	4 (3.4) 0	13 (30) 0
Serious AE	0	0	0	0
Discontinuation Drug-related	2 (1.7) 0	0 0	1 (1) 0	0 0

*Other OTG = 3 g 4.4% and 1 g 13.2% dose/formulation
[1]Mean duration of exposure (days): 1 g 10% OTG (23); 3 g 10% OTG (1); Other OTG (3); Oxytrol (11)
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 12, p. 27

Reviewer's comment: *No clinically significant or unexpected differences in safety were noted between different groups of comparison.*

7.1.1 Deaths

One death occurred in the entire safety database. A 54 year-old female subject (1039) 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, gastrointestinal [GI] bleed), according to a

medical examiner's autopsy report. The death was not considered to be treatment-related, and this reviewer agrees.

7.1.2 Other Serious Adverse Events

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 phase 3 study. Serious adverse events 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.

Reviewer's comment: *This reviewer reviewed all SAE case narratives and did not consider any SAE to be treatment-related.*

7.1.3 Dropouts and Other Significant Adverse Events

Phase 3 study (DB and OL periods): Overall, 47 of 789 patients (6.0%) withdrew from the study due to an adverse event. These 47 patients included 13 placebo-treated patients (13 of 400, or 3.3%) and 34 OTG-treated patients (34 of 496, or 6.9%). Of those who discontinued, 25 patients did so because of a treatment-related AE (7 placebo patients [1.8%] and 18 OTG patients [3.6%]). The most common drug-related AE's leading to premature discontinuation were application site reactions (12 OTG patients or 2.4%, 1 placebo patient or 0.25%), which accounted for approximately 50% of the patients who discontinued prematurely. These application site reactions included rash, pruritus, pustules, erythema, dryness, discoloration, hives, and papules and ranged from mild to severe in severity. Three patients (3/496 or 0.6%) reported the 5 severe application site reactions (11815-erythema x 2, 13528-pruritus, and 16601-urticaria, dermatitis) which led to the patients' discontinuation from the open-label extension.

- 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 was headache (4 patients in OTG [1%], 5 in placebo [1.25%]), followed by application site reactions (3 patient in OTG group [0.8%], 1 patient in 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 pruritus (4 patients) dermatitis (3 patients), dryness (3 patients), erythema (2 patients), pustules (2 patients), discoloration (1 patient), and papules (1 patient).
- Duration of active OTG treatment (< 12 weeks, ≥ 12 weeks): The discontinuation rates due to an AE's were similar for patients exposed to < 12 weeks (7.0%) and those exposed ≥ 12 weeks (6.4%). The discontinuation rates due to an adverse reaction was slightly higher in patients exposed to ≥ 12 weeks (4.6%) compared to those exposed < 12 weeks (3.4%). 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%).

***Reviewer's comment**: Among patients who received at least one dose of OTG treatment in the phase 3 study, there was a notable difference in the incidence of discontinuation due to application site reactions in the double-blind period (3 patients, 0.8%) compared to the open-label period (9 patients, 4.2%). During the open-label period, 5 patients randomized to placebo and 4 patients randomized to active OTG during the double-blind period discontinued because of application site reactions. Therefore, it appears that application site reactions significant enough to lead to study discontinuation can occur anytime during the course of OTG treatment. The average (SD) interval between initiation of active OTG treatment and onset of skin reaction that led to withdrawal was 59 (54) days (range 1-155 days).*

According to the sponsor, skin erythema scores for patients who discontinued because of application site AE's were "most commonly indicative of no erythema," which suggested that lack of erythema does not necessarily indicate acceptable skin tolerability. Furthermore, it was unclear if some of the significant application site reactions could be skin hypersensitivity reactions.

This reviewer reviewed the line listing of "Adverse Events Leading to Premature Discontinuation" and case narratives for all discontinuations in the double-blind and open-label periods of the phase 3 study (Study Report, Listing 14.3.2-3, Amendment 0004 dated August 27, 2008). In the double-blind period, 7 OTG patients discontinued due to adverse events considered by the investigator to be treatment-related (application site dermatitis, headache x 2, application site pruritus, dry skin/dry eyes/dry mouth, application site pruritus/dermatitis/headache, application site pustules, and constipation). There were two additional discontinuations in the active group that this reviewer considered to possibly be drug-related: patient 11904 discontinued because of dizziness and patient 12402 discontinued because of headache, although the investigator did not considered these AE's to be drug-related. In the double-blind and open-label phase 3 study, adverse reactions leading to premature discontinuation reported in > 1 OTG-treated patient are summarized in Table 30. Other adverse reactions leading to premature discontinuation among patients who received at least one dose of active OTG were (1 patient each): hypertonic bladder, dizziness, abdominal distension, hemorrhoids, abnormal LFT's, dry skin, dry mouth, dry eyes, application site erythema, application site discoloration, application site urticaria, and application site papules. Premature discontinuation due to anticholinergic adverse reactions was < 1%.

Table 30: **Adverse Reactions Leading to Discontinuation in Phase 3 Study (MO's Analysis)**

Preferred Term	OTG* N=496 n+ (%)	Placebo N=400 n (%)
Application site dermatitis	4 (0.8)	0
Application site pruritus	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.

Integrated phase 1 studies: 3 of 216 subjects (1.4%) discontinued due an adverse event (1 each for puncture site hematoma, urinary tract infection, and vomiting), none of which were considered related to treatment.

7.1.5 Common Adverse Events

TREATMENT-EMERGENT ADVERSE EVENTS:

- *Double-blind phase 3 study*: Adverse event rates were higher in OTG group than the placebo group (56.8% versus 48.3%). The most commonly reported AE's (>2% and greater than placebo) by MedDRA Preferred Terms were dry mouth, urinary tract infection, upper respiratory infection, dizziness, nasopharyngitis, application site pruritus, fatigue, and viral gastroenteritis. There were no significant differences in the incidence and frequency of AE's among patients ≥ 65 years old compared to younger patients.
- *Open-label phase 3 study*: The most common AE's were urinary tract infection, upper respiratory tract infection, application site dermatitis, application site pruritus, and urinalysis abnormal.
- *Duration of active OTG treatment*: Adverse events rates were slightly higher for patients treated for ≥ 12 weeks than those treated < 12 weeks (64.2% versus 56.3%).
- *Integrated phase 1 studies*: The most common AE's in the integrated phase 1 studies with the 10% OTG formulation were headache, dry mouth, dizziness, nausea, thirst, vomiting, pyrexia, and application site pruritus.

The most common AE's by Preferred Terms in the integrated phase 3 study are presented in Table 31, Table 33, and Table 34; and AE's in the integrated phase 1 studies are presented in Table 35. The AE's are discussed separately in the following order: double-blind phase 3 study, open-label phase 3 study, duration of active OTG treatment in the phase 3 study, and the integrated phase 1 studies.

Double-blind phase 3 study:

Table 31: Common Adverse Events (> 2% and > placebo) for Double-Blind Phase 3 Study

Preferred Term	1g 10% OTG N=389 n (%)	Placebo N=400 n (%)
Any AE	**221 (56.8)**	**193 (48.3)**
Dry mouth	29 (7.5)	11 (2.8)
Urinary tract infection	27 (7)	17 (4.3)
Upper respiratory tract infection	21 (5.4)	20 (5)
Dizziness	11 (2.8)	4 (1)
Nasopharyngitis	11 (2.8)	9 (2.3)
Application site pruritus	8 (2.1)	3 (0.8)
Fatigue	8 (2.1)	4 (1)
Gastroenteritis viral	8 (2.1)	7 (1.8)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 16, p. 31

Reviewer's comment: *No unexpected adverse events were noted based on the known safety profile of oxybutynin. Dry mouth, dizziness, application site pruritus, and fatigue are most likely to be treatment mediated and should be presented in product labeling. AE's of upper respiratory tract infection, nasopharyngitis, and viral gastroenteritis are unlikely to be treatment-mediated, and the higher incidences of these AE's in the OTG group are most likely due to chance. It is unclear if urinary tract infection is treatment-mediated.*

Reviewer's comment: *This reviewer conducted analyses of the various datasets (AF-AE.XPT, AF-DEMOG.XPT) to explore further details of AE findings in the double-blind phase 3 trial. The most common AE's for the overall study population in the double-blind phase 3 study are presented in Table 32. The incidences of application site reactions, dry mouth, urinary tract infection, and dizziness were notably higher in the OTG group than the placebo group. Some of the other known anticholinergic adverse effects (e.g., headaches, diarrhea, constipation) did not occur more frequently with active OTG treatment.*

Table 32: Common AE's (≥ 2%) in the Double-Blind Phase 3 Study (MO's Analysis)

Preferred Term	1g 10% OTG N=389 n (%)	Placebo N=400 n (%)	Overall N=789 n (%)
Headaches	24 (6.2)	28 (7)	52 (6.6)
Urinary tract infection	29 (7.5)	17 (4.3)	46 (5.8)
Dry mouth	29 (7.5)	12 (3)	41 (5.2)
Upper respiratory tract infection	21 (5.4)	20 (5)	41 (5.2)
Sinusitis	10 (2.6)	20 (5)	30 (3.8)
Application site reactions*	21 (5.4)	4 (1)	25 (3.2)
Diarrhea	11 (2.8)	13 (3.3)	24 (3.0)
Constipation	7 (1.8)	9 (2.3)	16 (2.0)
Dizziness	12 (3.1)	4 (1.0)	16 (2.0)

**Includes pruritus, dermatitis, papules, anesthesia, erythema, irritation, pain, and pustules*

This reviewer assessed the AE's by Preferred Terms that occurred > 1% and < 2% and greater than placebo in the OTG group. AE's meeting these criteria included: application site dermatitis (7 OTG patients [1.8%], 1 placebo patient [0.25%]) application site pruritus (6 OTG [1.5%], 5 placebo [1.2%]), peripheral edema (6 OTG [1.5%], 1 placebo [0.25%]), GGT increased (4 OTG [1%], 0 in placebo), ALT increased (4 OTG [1%], 3 in placebo). All but one case of peripheral edema was considered unrelated to treatment; the one treatment-related case was reported as "bilateral ankle edema" in a patient on active OTG. No meaningful conclusion can be drawn from these few cases of peripheral edema. The LFT elevations are discussed in detail in the "Laboratory" section of this safety review.

Because of known anticholinergic effects on the central nervous system (CNS), this reviewer evaluated specific CNS AE's by Preferred Terms. Compared to placebo, active OTG treatment was associated with higher incidences of dizziness (3% vs. 1%) and somnolence (0.8% vs. 0%). There was one case of syncope in the active OTG group; however, this AE did not appear to be treatment-related. In the double-blind phase 3 study, fifteen patients (7 OTG, 8 placebo) reported 15 AE's under the System Organ Class "Psychiatric Disorders." A majority of these AE's (12/15) were either insomnia (7) or anxiety (5). One OTG patient reported insomnia compared to 6 placebo patients. Four OTG patients (1%) reported anxiety compared to 1 placebo patient; all the anxiety AE's were mild except for one moderate AE of "anxiety secondary to pneumonia," and none led to drug discontinuation. Of the 15 AE's, 2 were considered to be treatment-related (insomnia in a placebo patient, anxiety secondary to pneumonia in an OTG patient). This reviewer does not consider the higher incidence of anxiety in the OTG group compared to placebo to be significant enough to be labeled, because anxiety is not an uncommon condition resulting from many different causes. There were no cases of hallucination, confusion, agitation, or dementia. There were no new significant neurologic or psychiatric adverse effects with OTG treatment.

Open-label phase 3 study:

Table 33: Common Adverse Events (≥ 2%) Open-Label Phase 3 Study

Preferred Term	OTG N=216 n (%)
Any adverse event	**97 (44.9)**
Urinary tract infection	19 (8.8)
Upper respiratory tract infection	10 (4.6)
Application site dermatitis	5 (2.3)
Application site pruritus	5 (2.3)
Urinalysis abnormal	5 (2.3)

Source: Study report, Table 12-7, p. 82

Reviewer's comment: *Of the 216 patients who entered the OL period, 13 patients or 6.0%, reported at least one application site AE's.*

Duration of OTG treatment in the phase 3 study:

Table 34: Common Adverse Events (≥ 2%) by Duration of OTG Treatment in Phase 3 Study

Preferred Term	OTG < 12 weeks N=387 n (%)	OTG ≥ 12 weeks N=109 n (%)	Overall N=496 n (%)
Any AE	**218 (56.3)**	**70 (64.2)**	**288 (58)**
Urinary tract infection	34 (8.8)	10 (9.2)	44 (8.9)
Upper respiratory tract infection*	19 (5)	10 (9.2)	29 (5.8)
Headache	13 (3.4)	8 (7.3)	21 (4.2)
Nasopharyngitis*	10 (2.6)	5 (4.6)	15 (3.0)
Application site pruritus	10 (2.6)	3 (2.8)	13 (2.6)
Sinusitis*	8 (2.1)	5 (4.6)	13 (2.6)
Diarrhea	7 (1.8)	5 (4.6)	12 (2.4)
Application site dermatitis	8 (2.1)	3 (2.8)	11 (2.2)
Bronchitis*	8 (2.1)	3 (2.8)	11 (2.2)
Gastroenteritis viral*	7 (1.8)	4 (3.7)	11 (2.2)

*No cases were considered by investigator to be treatment-related
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 18, p. 32-33

Reviewer's comment: *The incidence of application site pruritus and dermatitis do not appear to increase significantly with longer duration of OTG exposure. No other adverse events, other than headache and diarrhea, increased significantly with increasing duration of use.*

Integrated phase 1 studies

Table 35: Common Adverse Events (≥ 2% in OTG group) in the Integrated Phase 1 Studies

Preferred Term	Overall OTG* N=215 N (%)	Oxytrol TDS N=43 N (%)
Any AE	**73 (34.0)**	**15 (34.9)**
Headache	29 (13.5)	1 (2.3)
Dry mouth	13 (6)	0
Dizziness	9 (4.2)	0
Nausea	10 (4.7)	1 (2.3)
Thirst	9 (4.2)	0
Vomiting	6 92.8)	0
Pyrexia	6 (2.8)	0
Application site pruritus	5 (2.3)	4 (9.3)

*Inclusive of all OTG formulations, doses, and single-dose and multiple-dose studies
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 15, p. 30

Reviewer's comments: *The comparability of the integrated safety data between "overall" OTG and Oxytrol TDS is very limited due to differences in study design and scope of safety data.*

COMMON DRUG-RELATED ADVERSE EVENTS (ADVERSE REACTIONS):

- *Double blind phase 3 study:* More OTG patients reported at least one adverse reaction (AR) than placebo patients (19% versus 11%). These differences were primarily due to dry mouth (6.9% versus 2.8%) and application site reactions (5.4% versus 1%). See Table 36.
- *Open-label phase 3 study:* The most common adverse reactions were application site reactions (dermatitis, pruritus, dryness, erythema), which was reported by 13 patients (6%) and dry mouth (1.9%). See Table 37.
- *Duration of active OTG treatment (< 12 weeks, ≥ 12 weeks):* More patients treated with OTG for ≥ 12 weeks reported adverse reactions than those treated less than 12 weeks (20% versus 18%). Dry mouth, headache, and constipation occurred more commonly in patients exposed < 12 weeks of treatment than those exposed to ≥ 12 weeks of treatment. See Table 38.
- *Integrated phase 1 studies:* No unexpected AR's were observed. See Table 39.

Table 36: Common Adverse Reactions (≥ 1% in OTG group) in Double-Blind 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 pruritus	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)
Pruritus	5 (1.3)	5 (1.3)

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

Table 37: Common Adverse reactions (≥ 1%) in Open-Label Phase 3 Study

Preferred Term	OTG N=216 n (%)
Any adverse reaction	**22 (10.2)**
Any application site reaction	13 (6.0)
Application site dermatitis	5 (2.3)
Application site pruritus	5 (2.3)
Application site dryness	4 (1.9)
Dry mouth	4 (1.9)
Application site erythema	3 (1.4)

Source: Study report, Table 12-8, p. 82

Table 38: Common Adverse Reactions (≥ 1%) by Duration of OTG Treatment in Phase 3 Study

Preferred Term	OTG < 12 weeks N=387 n (%)	OTG ≥ 12 weeks N=109 n (%)	Overall N=496 n (%)
Any adverse reactions	**69 (17.8)**	**22 (20.2)**	**91 (18.3)**
Dry mouth	27 (7.0)	3 (2.8)	30 (6.0)
Application site pruritus	10 (2.6)	3 (2.8)	13 (2.6)
Application site dermatitis	8 (2.1)	3 (2.8)	11 (2.2)
Dizziness	5 (1.3)	1 (0.9)	6 (1.2)
Headache	5 (1.3)	1 (0.9)	6 (1.2)
Pruritus (non-application site)	4 (1.0)	1 (0.9)	5 (1.0)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 18, p. 32-33

Table 39: Common Adverse Reactions (≥ 2%) in Integrated Phase 1 Studies

Preferred Term	OTG* N=215 n (%)
Any adverse reactions	**58 (27.0)**
Headache	26 (12.1)
Dry mouth	13 (6.0)
Application site pruritus	5 (2.3)
Dizziness	5 (2.3)
Nausea	6 (2.8)
Thirst	9 (4.2)
Vomiting	4 (1.9)
Pyrexia	4 (1.9)

*Inclusive of all OTG formulations, doses, and single-dose and multiple-dose studies
Source: ISS, Table 15, p. 30

SEVERE ADVERSE EVENTS:
In the double-blind phase 3 study, 16 patients in OTG group (4.1%) reported 21 severe AE's and 16 patients in placebo group (4.0%) reported 16 severe AE's. The most common severe AE's were back pain (2 OTG patients, 0 placebo patients) and headache (2 OTG patients, 0 placebo patients). Three

patients experienced severe AE's considered to be treatment-related (2 OTG patients-headaches; 1 placebo patient-sinusitis). Both of the severe headaches in the OTG group led to premature discontinuation.

During the open-label phase 3 study, 9 patients (3 on DB OTG, 6 DB placebo), or 4.2%, reported an adverse event of severe intensity. Four of these 9 patients had severe AE's considered to be treatment-related, and these AE's included application site dermatitis, application site pruritus, application site erythema, application site urticaria, and dry mouth (1 each). Two patients discontinued due to these severe application site reactions.

No subjects in the integrated phase 1 studies reported any severe adverse events.

Reviewer's comment: *The data on severe application site reactions leading to drug discontinuation should be included in the OTG label.*

ADVERSE EVENTS AND SUBGROUPS

In the phase 3 study, no significant differences in the incidence or frequency of adverse events were noted between patients older and those younger than 65 years old. 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.

Reviewer's comment: *A review of the safety dataset showed that 53% of patients ≥ 65 years (149 of 283 patients) reported any AE's compared 52% of patients < 65 years old (265 of 506 patients. Among patients ≥ 65 years, 14% experienced at least one adverse reaction, the same incidence as those < 65 years old.*

ADVERSE EVENTS IN NON-INTEGRATED STUDIES

Of the 322 subjects in the 3 non-integrated studies, 296 received at least one dose of OTG (26 partners in the person-person transference study did not directly apply OTG onto their skin). A total of 113 subjects (38%) reported 183 adverse events. The most common drug-related AE's were related to application sites. Less than 10% (7 of 113) reported an anticholinergic adverse event, such as dry mouth or blurred vision. One death unrelated to treatment occurred in the dermatoxicity study OG05004 (see "Deaths" section). No patient experienced a non-fatal serious adverse event. Eight subjects discontinued due to adverse events, 5 of which were considered treatment-related: 2 subjects due to moderate diarrhea, 1 due to mild blurred vision, 1 due to application site irritation, and 1 due to application site pruritus. The remaining 3 subjects withdrew because of unrelated urinary tract infection, alcoholism (fatality in Study OG05004), and lower back pain.

1. **Cumulative irritation study (OG05003)**: 21 of 45 subjects (47%) experienced 34 AE's. Ten of these AE's were considered to be treatment related: 8 subjects reported 8 application site pruritus, 1 subject reported application site rash, and 1 subject reported application site pain.
2. **Repeat insult sensitization study (OG05004)**: 91 of 225 subjects (40%) experienced 148 AE's. One fatal SAE unrelated to treatment occurred in a 54 year-old female subject (1039) (see "Deaths" section). Treatment-related AE's included application site pruritus (5 subjects), application site warmth (4 subjects), diarrhea (3 subjects), blurred vision (1 subject), abdominal pain (1 subject), dry mouth (1 subject), dry throat (1 subject), and non-application site pruritus (1 subject).
3. **Transference study (OG06007)**: 1 of 52 subjects experienced an adverse event (myalgia).

***Reviewer's comment**: No unexpected adverse events or adverse reactions were noted in the non-integrated studies, although these studies were of limited duration (1-21 days) and, in study OG05004, subjects were exposed only to half the to-be-marketed dose.*

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program
Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were obtained at baseline and study exit only for phase 3 study OG05009 and phase 1 study OG02020. Laboratory testing was conducted only at baseline for other integrated phase 1 studies, and no laboratory testing was conducted in the 3 non-integrated studies. The following section discusses the laboratory results only from the phase 3 study with emphasis on the findings of the double-blind period.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*
No significant differences in laboratory parameters (hematology or chemistry) were noted with respect to mean laboratory values at baseline, at endpoint, and in changes from baseline between active treatment and placebo groups. Descriptive summaries did not reveal significant differences in the mean hematology or chemistry values between patients with < 12 weeks OTG exposure and those with ≥ 12 weeks exposure.

***Reviewer's comment**: This reviewer conducted independent analyses of the laboratory dataset and concurs with the sponsor's conclusions regarding the measures of central tendency.*

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*
In the double-blind phase 3 study, the proportion of patients with shifts from normal to abnormal (high or low) did not differ significantly between placebo and active treatment groups (Table 40). In the open-label phase 3 study, the proportion of patients with shifts outside the normal range did not differ significantly between patients randomized to placebo in the double-blind period (maximum OTG exposure 12 weeks) and those randomized to OTG in the double-blind period (maximum OTG exposure 26 weeks). See Table 41.

Table 40: Patients with Shifts from Normal to Abnormal in the Double-Blind Period

Laboratory	Placebo (N=400)	OTG (N=389)
Hematocrit		
Low	13 (3.5%)	13 (3.5%)
High	4 (1.1%)	7 (1.9%)
n	372	370
Bilirubin		
Low	0	0
High	1 (0.3%)	4 (1.1%)
n	375	370
AST*		
Low	0	1 (0.3%)
High	24 (6.4%)	29 (7.9%)
n	374	369
ALT**		
Low	3 (0.8%)	2 (0.5%)
High	33 (8.8%)	36 (9.7%)
n	374	370
GGT***		
Low	1 (0.3%)	1 (0.3%)
High	21 (5.6%)	21 (5.7%)
n	375	370
Triglycerides		
Low	0	0
High	26 (6.9%)	37 (10%)
n	375	369

* AST=aspartate aminotransferase ; ** ALT=alanine aminotransferase
** GGT=gamma-glutamyl-transferase
Source: Study OG05009, 14.3.5-5, p. 3221-9

Table 41: Patients with Shifts from Normal to Abnormal in the Open-Label Period

Laboratory	DB placebo (N=107)	DB OTG (N=109)	Overall (N=216)
Bilirubin			
Low	0	0	0
High	1 (1%)	1 (1%)	2 (1%)
n	101	103	204
AST			
Low	0	0	0
High	11 (11%)	12 (11.7%)	23 (11.3%)
n	100	103	203
ALT			
Low	0	0	0
High	8 (8.0%)	11 (10.7%)	19 (9.4%)
n	100	103	203
GGT			
Low	0	0	0
High	4 (4.0%)	8 (7.8%)	12 (5.9%)
n	101	103	204
Triglycerides			
Low	0	0	0
High	8 (7.9%)	12 (11.7%)	20 (9.8%)
n	101	103	204

Source: Study OG05009, 14.3.5-5, p. 3230-8

***Reviewer's comment**: There was a relatively high proportion of patients with abnormally high AST, ALT, and triglyceride in both placebo and active groups (approximately 10%) in the double-blind period. The same trend was observed in the open-label period where approximately 10% of patients had shifts from normal to abnormal in the same LFT parameters. These observed high proportions may be systematic laboratory phenomenon, because this is trend is also observed in the placebo group.*

7.1.3.3.3 *Marked outliers and dropouts for laboratory abnormalities*

Forty-six of 789 patients (5.8%) had changes in laboratory parameters that were considered to be clinically significant and that were reported as an adverse event, although none were considered as SAE.

***Reviewer's comment:** According to the sponsor, there were no protocol-defined criteria for laboratory changes that would qualify as "clinically significant." This assessment was made at the discretion of the investigator.*

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) changes that were considered to be "clinically significant." There were 7 events of clinically significant changes in LFTs (ALT increased, AST increased, GGT increased, liver function test abnormality, hepatic enzyme increased) in the placebo group compared to 23 events in the OTG group. It was unclear how many patients had each of these 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 LFT outliers and LFT AE's are discussed below:

LFT OUTLIERS:
According to the sponsor, 10 patients (8 OTG, 2 placebo) had changes in LFT's post-randomization that met at least one of the threshold criteria (ALT, AST, or GGT values > 3X ULN or a bilirubin value > 2X ULN). The findings are summarized in the following tables.

Number of subjects meeting or exceeding specified LFT thresholds

LFT parameters	OTG N=496	Placebo N=400
ALT or AST > 3X ULN	7	2
ALT or AST > 5X ULN	3	0
Bilirubin > 2X ULN	1	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	0
GGT > 3X ULN	5	1
GGT > 5X ULN	2	0

Subjects meeting or exceeding outlier LFT thresholds

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

***Reviewer's comment**: This reviewer evaluated the LAB.xpt dataset to assess how many subjects had outlier LFT values during the double-blind period and in the overall phase 3 study. The results follow*:

Number of patient with LFT outliers during the double-blind period (Visit 7/ET)*

LFT parameters	OTG N=389 n	Placebo N=400 n
ALT or AST > 3X and < 5X ULN	2	3
ALT or AST > 5X ULN	3	0
Bilirubin > 2X ULN	0	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	0

*Outlier values were observed at Week 7/ET

Number of OTG-treated patients with LFT Outliers during the phase 3 study (double-blind and open-label)*

LFT parameters	OTG N=496 n
ALT or AST > 3X and < 5X ULN	4
ALT or AST > 5X ULN	4
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.

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.

This reviewer 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.

Narratives of subjects with LFT changes of special interest are discussed below. The normal ranges for the LFT parameters follow: ALP (46-118 U/L), ALT (9-29 U/L), AST (12-31 U/L), bilirubin (0.1-1.0 U/L), and GGT (6-29 U/L).

***Bilirubin > 2X ULN (1 OTG patient)**: 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 (b)(4) which decreased to (b)(4) at Visit 7 (Week 12), and increased back to a level of (b)(4) at Visit 9 (Week 26). It was unlikely that the subject's hyperbilirubinemia was drug-related. Of note, the subject did not have liver transaminase (ALT, AST), GGT, or alkaline phosphatase elevation at any time during the study.*

***ALT or AST > 5X ULN (4 OTG patients)**:*

- *Subject 10401: This was a 57 year-old white female whose baseline LFT's were slightly elevated (ALT, GGT, and ALP). She completed 12 weeks of active OTG treatment during the double-blind period. During the study, she had adverse events of poison ivy and upper molar abscess and received the following therapies: methylprednisolone, betamethasone, kenalog, dexamethasone, amoxicillin, phenoxymethylpenicillin, ciprofloxacin, lidocaine, diazepam,*

cyclobenzaprine HCl, pethidine HCl, and vicodin. The investigator felt that her LFT elevations were most likely due to her "recent intake of vicodin and antibiotics per medical history." The patient's pertinent medical history included benign liver hemagioma (1998), coronary artery disease, and cholecystecomy (1993). Concomitmant therapies at study entry were potassium chloride, aceytlsalicilic acid, glyceryl trinitrate, isosorbide dinitrate, verapramil, and atorvastatin.

A summary of her LFT's follows:

Lab/Date	(b) (6)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *<u>Subject 10928</u>: This was a 50 year-old white female who entered the trial with slightly elevated GGT. She completed 12 weeks of active OTG treatment in the double-blind period. Her LFT elevation at the end of treatment was considered to be "clinically significant" and an AE of "increased liver enzymes" was reported for the patient. The investigator considered the AE to be unrelated to study drug and referred the patient to her primary physician. The patient's medical history was significant for cholecystectomy (1993), hypertension (2006), and hypercholesteremia (2006). Concomitant therapies at study entry included esomeprazole, atenolol, and rosuvastatin.*

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *<u>Subject 14520</u>: This was a 51 year-old white female with a history of Hepatitis C infection (diagnosed in 1980) who entered the study with elevated LFT's (ALT, AST, GGT). She completed 12 weeks of active OTG treatment in the double-blind period; all of her LFT values further increased at the end of the double-blind period. The patient participated in the open-*

label portion of the study for 1 day prior to the investigator's request that her study participation be discontinued due to the AE of elevated liver function tests that the investigator felt to be drug-related. Follow-up LFT's obtained 21 days after her last drug dose were within normal limits (WNL).

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *<u>Subject 15322</u>: This was a 66 year-old white female with slightly elevated LFT's (ALT, GGT) at study entry. She completed 12 weeks of placebo treatment, at which time her LFT's have further increased. She completed 14 weeks of active OTG treatment during the open-label period, at which time her LFT's were further elevated. These elevations were reported as adverse events that the investigator felt were drug-related. The patient's medical history was significant for cholecystectomy (1991) and hypercholesteremia (2003). Concomitant therapies at study entry included pantoprazole, metoprolol, inegy and ibuprofen.*

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

***Reviewer's assessment of LFT outliers**:*

- *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. Although ALT/AST elevations exceeding these thresholds are sensitive indicators of drug-related liver toxicity, they are relatively non-specific. There was no evidence of significant drug-related impairment of hepatic function (as*

indicated by no cases of drug-related clinically significant concurrent elevations in bilirubin and liver transaminase levels) in the relatively small safety database of OTG.

- *Drug-causality could not be 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).*
- *Although the safety database of OTG is too small to exclude drug-related liver toxicity, given the extent of exposure to oxybutynin in the past 30 years and the known systemic safety profile of oxybutynin, it is unlikely that OTG has significant potential of causing severe drug-induced liver injury.*

LFT ADVERSE EVENTS:
According to the sponsor, 20 AE's related to LFT changes were reported. The following table summarizes these 20 AE's:

	Placebo N=400		OTG N=496		Overall N=789	
Laboratory Abnormality	N (%)	Events	N (%)	Events	N (%)	Events
ALT increased	3 (0.8%)	3	5 (1.0%)	5	8 (1.0%)	8
AST increased	0 (0.0%)	0	2 (0.4%)	2	2 (0.3%)	2
GGT increased	0 (0.0%)	0	6 (1.2%)	6	6 (0.8%)	6
Liver function test abn	1 (0.3%)	1	3 (0.6%)	3	4 (0.5%)	4

***Reviewer's comment**: This reviewer conducted a review of the AE.XPT dataset and searched for all AE's related to liver function test abnormalities under MedDRA SOS of "Investigations." All of these AE's were treatment-emergent. The results follow:*

LFT AE's in Double-Blind Period (MO's analysis)

Preferred Term	OTG N=389 n (%)	Placebo N=400 n (%)
ALT increased	4 (1)	3 (0.75)
AST increased	0	0
GGT increased	4 (1)	0
LFT abnormalities	1	1
Hepatic enzyme increased	1	1
Blood bilirubin increased	0	1

LFT AE's in Double-Blind and Open-Label Periods (MO's analysis)

Preferred Term	OTG N=496 n (%)	Placebo N=400 n (%)
ALT increased	5 (1)	3 (0.75)
AST increased	1	0
GGT increased	6 (1)	0
LFT abnormalities	3	1
Hepatic enzyme increased	2	1
Blood bilirubin increased	0	1

During the double-blind period, 7 OTG patients (7/389 or 1.8%) and 6 placebo patients (6/400 or 1.5%) had at least one LFT abnormality that was considered to be an adverse event. Among the 496 patients who received at least one dose of OTG, 13 (or 2.6%) had at least one LFT abnormality considered to be an AE. The difference in the incidence of AE's related to LFT abnormality between OTG and placebo in the controlled portion of the study did not appear to be clinically significant.

PREMATURE DISCONTINUATION DUE TO LFT AE'S:

In the phase 3 study, two patients (Subjects 14505 and 14520) prematurely discontinued the open-label safety extension because of LFT elevations. Both of these patients received active OTG treatment during the double-blind period.

- Patient 14505 had a history of benign liver mass and entered the study with elevated baseline liver enzymes (ALT= (b) (4) AST (b) (4) GGT= (b) (4)). The LFT's further increased after 12 weeks of OTG treatment during the double-blind period (ALT= (b) (4), AST= (b) (4) GGT= (b) (4)). The patient entered open-label extension but was withdrawn 12 days later because of LFT elevations (ALT= (b) (4), AST= (b) (4) GGT (b) (4) A follow-up evaluation 43 days following the final gel application showed ALT, AST and GGT to have decreased to levels that the investigator no longer felt to be clinically significant. The total bilirubin levels were within normal limit (WNL) at all time points.

Patient 14505: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Open-label Day 12	Follow-up (43 days after final dose)
ALT	(b) (4)			
AST				
GGT				

Normal range for ALT (9-29 U/L), AST (12-31 U/L), GGT (6-29 U/L)

- Patient 14520 had a history of hepatitis C infection and had elevated baseline ALT ((b) (4) AST ((b) (4) and GGT ((b) (4)), which also further increased after 12 weeks of OTG treatment in the double-blind period (ALT= (b) (4) AST= (b) (4), GGT= (b) (4) The patient participated in the open-label safety extension for 1 day prior to being withdrawn because of LFT elevations. At a follow-up visit 21 days after the last OTG application, the ALT and AST levels had returned to normal and GGT level had fallen below baseline levels. The total bilirubin levels were WNL at all time points.

Patient 14520: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Follow-up (21 days after final dose)
ALT	(b) (4)		
AST			
GGT			

Normal range for ALT (9-29 U/L), AST (12-31 U/L), GGT (6-29 U/L)

***Reviewer's comment**: Patients 14505 and 14520 had underlying liver disease prior to the start of the study, and the* (b) (4)

(b) (4)

7.1.7.4 Additional analyses and explorations
No clinically relevant trends were noted for the clinical laboratory results based on geriatric status (< 65 years old versus ≥ 65 years old). The effects of gender and race on clinical laboratory parameters could not be assessed in a meaningful manner because of the limited number of male or non-Caucasian patients.

7.1.7.5 Urinalysis
Mean values, median values, and minimum and maximum for urinalysis pH and specific gravity with results expressed as percentage of Lower and Upper Normal Limit (calculated for each patient) and summary of abnormal (categorical analytes) urinalysis results at Endpoint were reviewed for differences between the 2 treatment groups. No significant findings were noted between active and placebo treatment groups at baseline and at the end of treatment.

7.1.7.6 Post-void residual
A post-void residual (PVR) urine volume was measured via ultrasound or catheter immediately after voiding at screening and at completion of double-blind phase 3 study. Overall, the mean PVR urine volume did not change across treatments and time. No significant increase in PVR urine volume was noted with OTG treatment.

Two patients with normal baseline values had PVR urine volume at end of treatment > 250 mL (one on OTG and one on placebo). An adverse event was reported for "increased post-void residual urine volume" for one patient on OTG treatment (14145) (Baseline (2/8/07) = (b) (4) mL, ET (2/26/07) = (b) (4) mL). The investigator did not consider this AE to be treatment related.

***Reviewer's comment**: Patient 14145 permanently discontinued study medication 14 days after the first dose of active OTG due to a 16-cm ovarian cystadenoma that required surgical intervention. Such a large ovarian cyst would have been present at the start of the study 14 days earlier, when the PVR volume was normal. It is unclear if this large ovarian cyst anatomically obstructed the bladder outlet leading to high PVR volume; alternatively, the high PVR volume may be secondary to an anticholinergic effect of OTG on increasing bladder storage capacity. A review of the line listing of PVR measurements for each patient on active OTG, however, did not indicate a trend of OTG use and elevated PVR urine volume.*

7.1.8 Vital Signs

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 *Analyses focused on measures of central tendencies*

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], temperature [T]): No clinically relevant trends in mean values or in mean changes from baseline to Endpoint were noted between placebo and active OTG groups, or between patients treated < 12 weeks compared to those treated ≥ 12 weeks.

***Reviewer's comment:** A review of the vital sign summaries by visit and treatment group for Study OG05009 showed no clinically significant differences in the mean or median SBP, DBP, or HR between the treatment groups.*

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*

In double-blind and open-label phase 3study, analyzing for change from baseline to Endpoint vital signs, a total of 3 patients treated with OTG had vital sign values that met pre-defined criteria for "clinically significant" changes in vital signs (1 diastolic, 2 systolic) compared to 2 patients (1 diastolic, 1 pulse) treated with placebo. In the integrated phase 1 studies, one patient in the showering study (OG06006) met the pre-defined criteria for vital sign changes (diastolic). In the non-integrated studies, no clinically significant changes were observed. No patient in the entire safety database discontinued prematurely because of vital sign changes.

Reviewer's comment: *In the phase 3 study, clinically significant changes were pre-defined as:*

- *SBP: Absolute change ≥ 20 mmHg AND endpoint SBP ≤ 90 mmHg or ≥ 180 mmHg*
- *DBP: Absolute change ≥ 15 mmHg AND endpoint DPB ≤ 50 mmHg or ≥ 105 mmHg*
- *HR: Absolute change ≥ 15 beats per minute (bpm) AND endpoint pulse ≤ 50 or ≥ 120 bpm.*

In the 74-Day letter, the Division requested the sponsor to analyze clinically significant changes in vital signs for the absolute change from baseline separately from those exceeding a pre-defined value for each clinic visit. The sponsor submitted these analyses to the NDA in Amendment 0004 dated to August 27, 2008. A detailed review of these analyses did not reveal any vital sign trends of safety concern. Overall, the incidence of vital sign outliers was similar between placebo and active groups and between patients treated with < 12 weeks and those treated ≥ 12 weeks across clinic visits.

7.1.9 Electrocardiograms (ECGs)

No specific QT study was performed. Safety ECG's were obtained at baseline and exit only during the double-blind phase 3 study. No trends toward change in ECG were noted in the phase 3 study. Overall, slightly higher proportion of placebo than OTG patients had ECG's that "worsened" from baseline (10% in OTG versus 13.1% in placebo). Nine ECG's (5 on OTG, 4 on placebo) were considered to be clinically significant.

Reviewer's comment: *A review of the ECG dataset (AF-ECG.XPT) was conducted to evaluate all study exit ECG's considered as "abnormal, clinically significant." In all, 8 placebo and 7 OTG patients had such ECG reading at study exit. Of these patients, 3 placebo and 4 OTG patients had "abnormal, clinically non-significant" baseline ECG's; 2 placebo patients and 1 OTG patient had "normal" baseline ECG. The incidence of clinically significant ECG changes in the OTG group was similar to placebo.*

7.1.12 Special Safety Studies

7.1.12.1 Skin tolerability

Local skin tolerability was assessed in the integrated 11 studies by visual inspection of the application area at variable time intervals post-application. Skin tolerability was graded based on the following erythema scale:

Erythema Scoring Scale

Score	Rating	Erythema at application site
0	None	None
1	Mild	Faint/barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

Double-blind phase 3 study: Application sites were evaluated for erythema changes at each clinic visit; 1466 and 1495 application sites were evaluated in the OTG and placebo groups, respectively. The results across all visits in DB period are summarized in Table 42.

Table 42: Erythema Assessment in Double-Blind Phase 3 Study

Erythema Assessment (# of evaluations)	OTG (1466)	Placebo (1495)
Mild	14 (1.0%)	13 (0.9%)
Moderate	5 (0.3%)	0
Severe	0	0

Source: Summary of Safety, Module 2.7.4, Table 2.7.4-18, p. 29

Duration of active OTG treatment: 1634 application sites were evaluated in patient with < 12 weeks OTG treatment and 620 application sites in patients with ≥ 12 weeks of treatment. The findings across all visits by duration of treatment group are summarized in Table 43.

Table 43: Erythema Assessment in Phase 3 Study by Duration of OTG Therapy

Erythema assessment (# of evaluations)	< 12 weeks (1634)	≥ 12 weeks (620)	Overall (2254)
Mild	15 (0.9%)	6 (1.0%)	21 (0.9%)
Moderate	4 (0.2%)	2 (0.3%)	6 (0.3%)
Severe	0	0	0

Source: Summary of Safety, Module 2.7.4, Table 2.7.4-19, p. 29

Integrated Phase 1 studies: Table 44 summarizes the findings of application site erythema assessments in the 10 integrated phase 1 studies in healthy volunteers. Erythema assessments were conducted 1 and 24 hours post-application.

Table 44: Erythema Assessment in the Integrated Phase 1 Studies

Erythema evaluation	All OTG Erythema events/ # of evaluations (%)	Oxytrol TDS Erythema events/ # of evaluations (%)
Mild		
1 hr	0/372	8/41 (20)
24 hr	1/565 (0.2)	4/41 (9.8)
Moderate		
1 hr	0	0
24 hr	0	1/41 (2.4)
Severe		
1 hr	0	1/41 (2.4)
24 hr	0	0

Source: Clinical Summary, Module 2.7.4, Table 2.7.4-17

Reviewer's comment:

- *There were no cases of severe erythema in the protocol-defined assessments. However, one patient who discontinued prematurely because of an application site reaction had severe erythema (11815). The incidence of any erythema was minimal (≤ 1%).*
- *Erythema changes did not appear to worsen significantly with longer duration of drug exposure.*

***Reviewer's comment**: Although OTG treatment had minimal erythema changes, the sponsor's erythema scoring system is a limited assessment of local skin tolerability. Local skin reactions, such as edema, induration, and other changes are not captured by this scoring system. The results of the erythema evaluation should be combined with the application site adverse reaction data to better assess skin tolerability of OTG.*

- *During the double-blind phase 3 study, 21 or 5.4% OTG patients versus 4 or 1% placebo patients reported at least one application site reaction. Less than half of these OTG patients (8 of 21) had any erythema changes. During the open-label phase 3 study, 6% of patients reported at least one application site reaction.*
- *Among patients who received at least one dose of active OTG (either in the double-blind or open-label period or both), 6.7% reported at least one application site reaction.*
- *In the double-blind and open-label phase 3 study, 2.4% of OTG-exposed patients (compared to 0.8% of placebo) discontinued prematurely because of an application site reaction. A majority of patients who discontinued because of an application site reaction did not have erythema changes.*
- *Compared to patients treated with OTG < 12 weeks, more patients who received OTG ≥ 12 weeks reported at least one application site reaction (8.3% versus 6.2%) and more discontinued because of an application site reaction (3.7% versus 2.1%).*
- *Common application site reactions were pruritus (most common), dermatitis (second most common), erythema, and papules.*

Although there are no clinical trials directly comparing the skin tolerability of the 2 transdermal oxybutynin products, controlled clinical trial data indicate that the skin tolerability of OTG appears to be better than Oxytrol. According to a clinical review of the Oxytrol NDA (NDA 21-351/S000), of the 3173 application sites evaluated in OAB patients treated with Oxytrol, 36% showed mild erythema, 14% showed moderate, and 0.8% showed severe erythema compared to ≤ 1% with OTG in Study OG05009. In the phase 3 clinical trials of Oxytrol, approximately 23% of patients on active treatment reported at least one application site reaction compared to 6.7% of OTG-exposed patients in OG05009. In the Oxytrol trials, 7-9% of patients treated with active Oxytrol discontinued prematurely because of an application site reaction compared to 2.4% of OTG-exposed patients in OG05009

7.1.12.2 Dermatoxicity

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. The objective was to evaluate the incidence and severity of cumulative skin irritation. 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.

***Reviewer's comment:** The sponsor evaluated the potential cumulative irritant effect of placebo and active (1 g 10% OTG) gels in New Zealand White rabbits (ONY00012). Under the test conditions, both placebo and active gels were considered to be non-irritants.*

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 10%. 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-minute, 24-hour, 48-hour, and 72-hour after gauze removal.

***Reviewer's comment**: Skin hypersensitivity to OTG 10% should be adequately labeled in the Warnings and Precaution section of the label. Patients who experience skin hypersensitivity to OTG should discontinue treatment. Furthermore, because patients with drug-related skin hypersensitivity may rarely experience systemic hypersensitivity when re-challenged with the active drug, caution should be used when starting these patients on other oxybutynin products.*

Because the dose-dependence for skin sensitization with OTG is unknown, it is unclear if the incidence of skin hypersensitivity using 0.5 g of OTG would be the same as the 1 g dose. To err on the conservative side, this reviewer considers the skin hypersensitivity incidence of 0.5% observed in Study OG05004 to be a low estimate for 1 g 10% OTG.

The dermal sensitization potential of placebo and active gels was evaluated in Hartley-derived albino guinea pigs (ONY00013). Under the test conditions, both active and placebo gels were not considered to be contact sensitizers.

7.1.12.3 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 from 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 Cmax = 0.94 ng/mL, mean AUC [0-48 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 Cmax =0.02 ng/mL) starting at 8 hours post-dose and which were still detectable at 48 hours post-dose.

***Reviewer's comment**: 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 can be adequately addressed in the product label.*

7.1.14 Human Reproduction and Pregnancy Data

Two pregnancies occurred during the clinical trials with OTG. In Study OG05003 (21-day cumulative skin irritation study), Subject 844 had a positive urine pregnancy test on (b) (6), following (b) (6) consecutive daily applications of 1 g OTG 10%. The subject carried the pregnancy to term and delivered a healthy, full-term baby on (b) (6). No maternal or fetal complications were reported. In Study OG06005 (comparative steady state PK of 1 g 10% OTG and Oxytrol TDS), Subject 1308 had a positive urine pregnancy test on (b) (6), following 18 days of treatment with Oxytrol oxybutynin transdermal system (3.9 mg/day) and (b) (6) days of daily treatment with 1 g 10% OTG. The subject was lost to follow-up. According to the sponsor, a third party reported that the subject carried the pregnancy to term and delivered a healthy baby on (b) (6).

Oxybutynin is a Pregnancy Class B based on preclinical data showing no evidence of impaired fertility or harm to the animal fetus. There are no human pregnancy data with oxybutynin.

7.1.16 Overdose Experience

According to oxybutynin product labels, overdosage with oxybutynin has been associated with anticholinergic effects, such as central nervous system excitation, dehydration, cardiac arrhythmia, and urinary retention.

Although no clinical overdose experience exists with OTG, plasma concentrations of oxybutynin decline starting at 24 hours after gel application. Patients should be monitored accordingly.

7.2.9 Additional Submissions, Including Safety Updates

The following additional sources were reviewed for safety information related to transdermal oxybutynin:

- *120-Day Safety Update*: This safety update covers the period of January 1, 2008, to July 15, 2008. The sponsor had no additional clinical safety update to report during this safety update time period.
- *Annual report for IND 67,126* (OTG for the treatment of OAB): This annual report covers the period from April 1, 2007, to March 31, 2008. No new or unexpected safety information was noted.
- *Periodic Adverse Drug Experience (ADE) Annual Report for NDA 21-351 (Oxytrol TDS 3.9 mg/day) supplemented with this reviewer's AERS database reports*: This annual report covers the period from February 26, 2007, through February 25, 2008. There were 2 notable ADE reports:

    1. 15-Day Safety report (MedWatch report #5390808): a 67 year-old female started treatment with Oxytrol TDS for U-UI on June 17, 2007. (b) (6) days later, she experienced "global transient amnesia" for 6 hours associated with a fall. Her diagnostic workup (brain CT, EKG, carotid Doppler, EEG) was normal. She has no significant medical history and concomitant medications included estrogen cream (Premarin), zopiclone (Imovane), and mometasone furoate nasal spray (Nasonex). The patient was treated and discharged from the emergency room. The patient discontinued treatment with Oxytrol, although no other follow-up information was available.

2. 15-Day Safety report (MedWatch report #5606632): a 60 year-old female experienced "aphasia, slow speech, and showed signs of anticholinergic overdose after applying her first Oxytrol patch" on (b) (6). Her husband reported that she woke up from her sleep and was found on the floor "confused, drowsiness/somnolence, dry mouth, and inability to talk/word finding difficulties." The patient may have fallen but did not lose consciousness. Her diagnostic workup in the emergency room was normal (vitals, laboratory tests, EKG, CT of the head, chest X-ray, cardiac enzymes). She was admitted for observation overnight, treated symptomatically, and discharged the following day with resolution of her symptoms. She discontinued Oxytrol treatment while in the emergency room. The patient has no significant medical history and the report indicated that "her routine home medications were continued," although concomitant medications were not listed. The report also indicated a diagnosis of "possible drug reaction with Oxytrol."

Reviewer's comment: *Drug-causality cannot be ruled out in both of the above cases. However, given that there were only 2 cases of notable neurological impairment (out of estimated 390,000 new prescriptions in the U.S. during the reporting period), this reviewer does not believe this reporting frequency rises to the level of safety labeling for all transdermal oxybutynin products.*

A review of other periodic ADE reports indicate that there were 1 serious AE of "visual hallucination," and one report of "hallucination," 2 cases of "confusional state," and 6 cases of "balance disorder." Many of these AE's occurred in the setting of other concomitant medical conditions (e.g., Parkinson's disease, stroke, dizziness), although the psychiatric and neurologic adverse effects of antimuscarinic therapy, especially oral oxybutynin, is known. This reviewer does not believe these reporting frequencies rise to the level of safety labeling for all transdermal oxybutynin products.

- *Annual Report for NDA 21-351 (Oxytrol TDS 3.9 mg/day):* No new safety findings were noted.

7.3 SAFETY CONCLUSIONS

- The safety profile of OTG 10% is overall acceptable with the expected anticholinergic systemic effects of a transdermal oxybutynin product. Although no studies directly comparing the 2 transdermal products exist, the skin tolerability of OTG 10% appears to be better than that of the oxybutynin transdermal system (Oxytrol TDS).
- Contact hypersensitivity to OTG reactions occurs at an incidence of 0.5%.
- 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.

8 ADDITIONAL CLINICAL ISSUES

8.1 DOSING REGIMEN AND ADMINISTRATION

The to-be-marketed dose and dose regimen is a fixed regimen of 1 g 10% OTG applied once a day. This dose was based on PK similarity with Oxytrol TDS. No other doses or dose regimens were evaluated for clinical safety and efficacy in the clinical development of OTG.

8.2 DRUG-DRUG INTERACTIONS

No drug-drug interaction (DDI) studies were conducted with OTG. This reviewer does not consider any specific DDI study with OTG to be necessary at this time.

8.3 SPECIAL POPULATIONS

Geriatrics: In the phase 3 study, approximately 35% of patients were at least 65 years old. No clinically differences in safety or efficacy were noted between these patients and younger patients. This reviewer does not consider dose adjustment in patients ≥ 65 years old to be necessary.

Pediatrics: OTG has not been evaluated in individuals younger than 18 years of age. In the original NDA submission dated March 26, 2008, the sponsor requested a waiver of pediatric studies in children under the age of five and a deferral of pediatric studies in children ages 5 to 17 years until after the approval of OTG for use in the adult population.

In Amendment 0005 dated September 11, 2008, submitted to the NDA, sponsor submitted a proposed Pediatric Protocol Synopsis for the deferred pediatric population. The Pediatric Plan relies extensively on the findings of Study OGO03010, which the sponsor conducted in response to a BPCA Written Request for Oxytrol TDS dated May 14, 2004. The sponsor proposed an open-label, uncontrolled, PK and safety study in 40 children ages 5-15 years with detrusor overactivity associated with a neurological condition to bridge to the findings of Study OG03010. In a letter dated November 18, 2008, the Division informed the sponsor that a clinical safety and efficacy trial in the deferred pediatric population would be necessary. In Amendment 008 dated December 5, 2008, the sponsor proposed a trial evaluating the safety and efficacy of OTG in children ages 5-15 with urinary frequency and daytime incontinence NOT due to a neurologic condition. The Division informed the sponsor in a teleconference on December 18, 2008, that a pediatric population where the potential benefits of an anticholinergic therapy may outweigh the risks is children with neurogenic bladder. The Division advised the sponsor to submit a pediatric plan outlining a dose-finding PK/PD study in the deferred pediatric population and a clinical safety and efficacy study in the same population. In response, the sponsor submitted a revised pediatric plan for the deferred population outlining a PK/PD dose-finding study in approximately 30 children with neurogenic bladder followed by a safety and efficacy study in 60 children with neurogenic bladder. The final study reports of these 2 studies would be submitted to the FDA by September, 2012 (PK/PD study) and August, 2015 (safety and efficacy study). Although the Division did not agree to any specific details of the study synopses and this was conveyed to the sponsor during the labeling negotiation teleconference on January 13, 2009, the revised pediatric plan was sufficient for the Division to recommend a deferral of the pediatric studies in children ages 6 to 16 years, 11 months. PeRC concurred with the Division's recommendation.

Gender/Race: The number of patients in the phase 3 study who were male or non-Caucasian was too limited to draw any meaningful conclusions about the effect of gender or race on the safety or efficacy of OTG.

Hepatic or Renal Impairment: The pharmacokinetics of OTG was not evaluated in patients with renal impairment or liver insufficiency.

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS

In summary, the treatment benefits outweigh the risks for 1 g 10% OTG once daily in adults with symptomatic overactive bladder not related to pathological or metabolic disorders or medication use. Study OG05009 demonstrated that OTG treatment resulted in statistically significant improvement in the primary endpoint (number of daily urinary incontinence episodes) and the key secondary endpoint (urinary frequency) compared to placebo after 12 weeks of treatment. The improvement in these clinical endpoints was clinically meaningful. The safety and tolerability profile of 10% OTG was generally consistent with the known adverse event profile of the oxybutynin transdermal system (Oxytrol TDS) and other oxybutynin products. The skin tolerability of 10% OTG, however, appeared to be better than that of the oxybutynin transdermal system (Oxytrol TDS). Two main safety issues with OTG were the definite potential for dermal transfer of oxybutynin with direct skin-to-skin contact at the application site and skin sensitization. Both of these issues, however, can be adequately addressed in the product label.

9.2 RECOMMENDATION ON REGULATORY ACTION

From a clinical perspective, this reviewer recommends the approval of this NDA pending the Office of Compliance's recommendation regarding the acceptability of the manufacturing sites.

9.3 RECOMMENDATION ON POSTMARKETING ACTION

This reviewer recommends routine post-marketing surveillance. All suspected skin sensitization reactions should be reported as 15-Day Reports.

9.4 LABELING REVIEW

The following major clinical labeling changes are recommended and have been made othte proposed label:

1. Highlights of Prescribing Information:

a. Indications and Usage: The word "antispasmodic" in the description of the pharmacologic class of OTG is not a well-recognized pharmacologic class and should be deleted.

b. Warnings and Precautions:
   - Safety information on the risk of skin sensitization, potential for skin transference with OTG, and flammable alcohol-based gel should be included.

2. Full Prescribing Information

a. Contraindications (Section 4): OTG should be contraindicated in patients who experience hypersensitivity, including skin sensitization, to the product.
b. Warnings and Precautions (Section 5): This section should include safety information on skin sensitization and skin transference.
c. Adverse Reactions (Section 6): This section should contain general clinical summary of the adverse reaction profile and adverse reactions which led to study withdrawal. Table 1 should reflect common AE's where the incidence in the OTG group is > 2% and > placebo to present the AE data in balanced manner without judgment as to drug-causality. The safety data on application site reactions should also be presented.
d. Clinical Studies (Section 14):

i. The results of the Incontinence Impact Questionnaire (IIQ) and King's Health Questionnaire should not be included in the product label. Both of these endpoints, which are not included in any other OAB product labels, are considered exploratory, and have not been adequately validated for labeling claims.

10 APPENDICES

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS

10.1.1 Appendices of Study OG05009

a. Schedule of Events for Screening, Double-Blind, and Open-Label Periods

Assessments	Screening/Baseline Period				Double-Blind Treatment				Open-Label Treatment	
	Initial Evaluation	Wash-out	Start of Baseline	End of Baseline						
Patient Visits	V_1	2-week Washout/Training Period	V_2	V_3	V_4	V_5	V_6	V_7/ ET	V_8	V_9/ET
Weeks	-3		-1	0	1	4	8	12	19	26
Informed Consent	X							X		
Medical History	X									
Physical Examination			X					X		
Concomitant Medications	X		X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X
Urinalysis			X					X		X
ECG			X or	X				X		
Serum Chemistries[1]			X					X		X
CBC			X					X		X
PSA (Males only)			X							
Urine beta-HCG[2]				X				X		X
3-Day Urinary Diary[3]				X	X	X	X	X		
2-Day Voided Volume[4]				X	X	X	X	X		
PVR				X				X		
QoL Questionnaires				X	X	X	X	X		X
Plasma Concentration					X	X	X	X		
Study Drug Dispensed				X		X	X	X[5]	X[5]	
Daily Gel Application					X	X	X	X	X	
Skin Tolerability Assessment					X	X	X	X	X	X
AE Assessment					X	X	X	X	X	X

[1] Fasting

[2] Urine beta-HCG tests was only performed for female patients of child-bearing potential

[3] A 3-day (consecutive days) urinary diary was recorded during the week immediately prior to the indicated visit beginning at least 4 days prior to the visit.

[4] During two consecutive days of the 3-day diary, patients were required to collect all urine during normal voids and record the voided volume on the diary card.

[5] Patients in open-label extension only

Source: Study report, Table 9-3, p. 27

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b. Eligibility Criteria

Inclusion:

1. Male or a non-pregnant, non-lactating female using adequate means of birth control, if not menopausal
2. At least 18 years of age
3. History of overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency, with or without neurological disease
4. Recorded an average of ≥ 8 urinary voids per day and ≥ 4 urge urinary incontinence episodes during the 3-day baseline diary period
5. Average recorded urine void volume of ≤ 350 mL per void during the 2-day urine collection of the 3-day baseline urinary diary
6. History of pure urge or mixed urinary incontinence with a predominance of urge incontinence episodes (on baseline diary)
7. Post-void residual urine volume of ≤ 250 mL, as measured by ultrasound or catheterization
8. Capable of completing the urinary diary without assistance

Exclusion: Patients were excluded from participation based on the criteria outlined in the protocol. These criteria were established primarily to exclude patients whose incontinence may have been related to chronic illness, anatomical weakness/abnormalities or concomitant medications.

1. Did not complete all 3 days of the 3-day urinary diary during the baseline assessment
2. History of lower urinary tract surgery within the past six months
3. Continuous small volume urine loss/leakage
4. Clinically significant systemic disease or condition that would, in the investigator's opinion, lead to undue risk following administration of oxybutynin
5. Laboratory value(s) outside the normal range that were, in the opinion of the investigator, clinically significant and could interfere with the patient's participation or outcome/interpretation of the study
6. History of alcohol/drug abuse within the past year
7. Known hypersensitivity to oxybutynin or related compounds, or any component of the gel formulation
8. Active skin disorder, such as eczema, seborrhea, or psoriasis affecting the gel application areas
9. Known uncontrolled narrow angle glaucoma
10. One or more treatable conditions that may cause urinary incontinence or urgency (e.g., urinary tract infection, prostatitis, hematuria, urinary tract obstruction, urethral diverticulum, bladder tumor, bladder stone, prostate cancer, fecal impaction, requirement for acute or intermittent use of diuretics, excessive use of alcohol) [Note: Patients with acute urinary tract infection may have been treated for infection and then re-evaluated for entry into the study.]
11. Diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome
12. Gastrointestinal conditions such as partial or complete obstruction, pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic), decreased gastrointestinal motility (paralytic ileus, intestinal atony, chronic and severe constipation), or risk of gastric retention
13. Male patient with a PSA > 4 ng/mL. Patients with PSA ≤10 ng/mL and negative prostate biopsies within 1 year prior to study entry were acceptable (Note: Patients who had undergone a prostate biopsy within the previous 3 months were not eligible)
14. History of prostate biopsy positive for prostate carcinoma
15. History of significant medical problems that could have confound the outcome of the study (e.g., > 3 urinary tract infections within the past 12 months, unstable diabetes mellitus, anticipated changes in hormonal status [patients receiving hormone treatments were requested to maintain the same hormone treatment regimen throughout the study period])

16. Diagnosis of overflow incontinence secondary to under active or acontractile detrusor or outlet obstruction, or other evidence of significant outlet obstruction (including benign prostate hyperplasia)
17. Required concomitant medications that may affect detrusor activity, including tricyclic antidepressants (e.g., imipramine, doxepin, desipramine, and nortriptyline)
18. Excessive consumption of caffeine (> 5 cups of coffee, tea, or cola daily)
19. Could not maintain usual program of nonpharmacologic management of incontinence (e.g., pelvic floor exercise and timed voiding/bladder training) during the study
20. Participated in another investigational drug study within 30 days prior to the first study drug administration
21. Judged by the investigator to be unsuitable for enrollment in this study for any reason

10.1.2 Study OG05003

Study Title: "A 21-day cumulative irritation study of topically applied oxybutynin gel and placebo gel in healthy volunteers"

Study period: October 2005-November 2005

Objective: To calculate the incidence and evaluate the degree of cumulative skin irritation associated with repetitive 24-hour applications of active and placebo Oxybutynin Topical Gel to the same sites during a 21-day study period

Study design and conduct: This study was a single-center, evaluator-blinded, multiple-application study. Subjects received applications of the two gels daily (1 g OTG 10% gel and matching 1 g placebo gel), applied to the same application sites on the back and then covered with a 4 x 4 inch gauze pad for 24 ± 2 hours over the 21-day period. A left and right application site on the back was randomized for treatment with active or placebo gel for each subject for the duration of the study. Subjects reported to the clinic for daily gel application and dermatologic evaluations on an outpatient basis. Dermatologic evaluations were performed prior to the first system application, at the time of removal of each gauze pad, and approximately 24 hours following the final pad removal. The dermal evaluators were blinded to the application sites of the test and control systems. Safety evaluation consisted of monitoring adverse events.

Reviewer's comment: *The Cumulative Skin Irritation Study design usually calls for occluded applications to detect irritation under maximum stress conditions. Study OG05003 investigates the cumulative irritation potential of OTG 10% under modified conditions of maximal stress. Rather than using the occlusive patch, the study used an open patch method to better simulate conditions of therapeutic use. The Division previously agreed that such modification was acceptable for a topical gel.*

Otherwise, the remainder of the general study design and conduct of OG05003 are consistent with the Agency's recommendations for a Cumulative Skin Irritation Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).

Summary of study schedule:

PROCEDURE	SCREEN	DAY 1	DAY 2 to 21	DAY 22	DAY 23
Informed Consent	X				
Urine Pregnancy Eval.[1]	X	X			X
Medical/Drug History	X				
Physical Examination	X				
Gel Applications		X	X		
Dermatologic Evaluation[2, 3]		X	X	X	X
Concomitant Medication Use		X	X	X	X
Adverse Event Monitoring		X	X	X	X

[1] *For female subjects of child-bearing potential at screen, prior to first dose and at exit from study*
[2] *Before initial application and following removal of each gauze pad and 24 hours post removal of final pads*
[3] *Photographs will be taken only if grade 3 skin reaction is present.*

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Eligibility criteria:
Inclusion:

- Male or female, 18 to 65 years old
- Provide written informed consent
- Willing to use an acceptable method of birth control during study participation

Exclusion:

- Pregnant or nursing (females only)
- Contraindications to oxybutynin therapy or intolerance of other anticholinergic medications
- Hair, tattoos, pigmentation, scars, moles or other conditions at the area of gel applications that may interfere with applications, tolerability, or post-application evaluation
- Clinically significant skin condition at application sites that contraindicates participation, including psoriasis, eczema, atopic dermatitis, and active cancer within one year
- Participation in a Draize-type patch test or cumulative irritation test within the past 4 weeks
- Participation in a primary irritation test or soap chamber test within the past 4 weeks
- Participation in a clinical trial or receipt of an investigational medication within 1 month of the study
- Routine use of anti-inflammatory, immunosuppressive or antihistamine medications (81 mg of aspirin daily for cardiovascular prophylaxis was allowed)
- Allergy injections
- Health history including any one or combination of these diagnosis: severe asthma, active immunologic disorders, insulin dependent diabetes, glaucoma
- Clinically significant chronic illness which could place the subject at increased risk during participation or result in inappropriate dermal response during the study
- History of alcohol or drug abuse within 1 year of the study
- Inability to provide written informed consent
- Judged by the investigator to be unsuitable for any reason

Evaluation variables:
The skin potential of the gel systems was evaluated in terms of cumulative irritation. The cumulative irritation score was determined for each subject using the following score system by Berger and Bowman described in Table 1. A numeric score was assigned when a clinically significant skin response was noted or ≥ 25% of the test site area showed a skin response.

Table 1: Scoring Scale of Berger and Bowman

Skin response	
Dermal reactions	**Numeric score**
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible or minimal edema or minimal papules	2
Erythema and papules	3
Definite erythema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test site	7
Response of superficial layers of the skin	
Surface skin reactions	**Letter score (equivalent numeric score)**
Slight glazed appearance	A (0)
Marked glazing	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudate covering all or portion of the test site	G (3)
Small petechial erosions and/or scabs	H (3)

***Reviewer's comment**: The above scoring system was one example of an acceptable scoring system to quantify skin reactions in a Cumulative Skin Irritation Study or a Skin Sensitization Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).*

Statistical consideration:

Sample size: A sufficient number of healthy subjects were enrolled to ensure that 30 subjects complete the study. This is a standard sample size for a 21-day cumulative irritation study.

Analysis population: The cumulative irritation evaluation analysis will be based on the Evaluable population, which consisted of all subjects who completed the study and those withdrawn due to skin reaction score of ≥ 3. The Evaluable population did not include subjects who discontinued prematurely for other reasons. Safety analysis will be based on the Safety population, which included all subjects who received at least one dose of study drug.

Cumulative irritation analysis: The actual test score consisted of a combination of the numeric and letter grades (described by the Berger and Bowman scoring system). Letter grades were converted into numerical equivalents: A=0; B=1; C=3; and F, G, and H = 3. These numeric equivalents are additive to a

numerical score. The cumulative irritation score was determined for each subject by treatment. An individual score of 3 will be carried forward for any discontinued subject for the remaining evaluation time points. Descriptive statistics on individual scores were provided by treatment and application day. The total cumulative irritation score was summarized using descriptive statistics. For the calculation of total score, an upper limit of 3 was selected for reaction scores > 3. According to the sponsor, it would be meaningless to use a score > 3 (extreme irritation) because the "intent of this test is to compare treatments that are relatively mild." The total cumulative irritation score was normalized to a base of 10 average. The irritation of test and control systems was classified according to an empirically derived categorization system described below:

Classification system of interpretation of Base 10 Irritation Scores

Score	Class	Indications from Test	Description of Observed Responses
1	0-49	Mild article - no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e., continuous reapplication and occlusion at concentration specified).
2	50-199	Probably mild in normal use	Evidence of a slight potential for very mild cumulative irritation under conditions of test.
3	200-449	Possibly mild in normal use	Evidence of a moderate potential for mild cumulative irritation under conditions of test.
4	450-580	Experimental cumulative irritant	Evidence of a strong potential for mild to moderate cumulative irritation under conditions of test.

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This classification system is designed to differentiate the irritation potential of relatively mild test materials.

***Reviewer's comment**: The sponsor used the same cumulative irritation analysis and classification system of interpretation for the irritation potential with the oxybutynin transdermal system (Oxytrol TDS). According the medical officer's review of the Oxytrol NDA, active transdermal system produced a Class 4 irritation score and placebo transdermal system produced a Class 3 score.*

Subject Disposition:
A total of 45 subjects (14 males, 31 females) were enrolled and 41 subjects completed the study. One subject withdrew due to unrelated adverse event (lower back pain) and 3 other subjects withdrew due to personal reasons (schedule conflict).

Demographics and baseline characteristics:
Subjects were primarily non-Hispanic (93%) White (100%) men (30%) and women (70%) with an average (SD) age of 36 (12) years.

Cumulative Irritation Analysis:
The Evaluable population consisted for 41 subjects. 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.

***Reviewer's comment**: A review of the skin assessment actual visual scores at each visit (table 14.2, p. 37 of study report) was conducted. One subject (subject #8) had severe irritation (score of 7) after the 3rd dose on both the placebo and active gel sites. This patient was withdrawn from the study and a converted*

score of 3 was carried forward in the cumulative irritation analysis. No other subject had an actual irritation score ≥ 3 at any skin evaluation. Six subjects (2, 3, 11, 27, 30, 43, or 13%, had a skin evaluation with a score of 2 at the OTG site; 2 subjects (26, 32), or 4%, had a skin evaluation with a score of 2 at the placebo site.

Safety analysis:

- *Extent of exposure*: Forty subjects received all 21 applications. One subject received 2 doses prior to scoring an irritation score of 7 and was withdrawn. Four other subjects received 1-13 applications prior to discontinuing the study for reasons unrelated to treatment.

- *Adverse events*: No deaths or non-fatal serious adverse events occurred. A total of 21 subjects (47%) reported 34 adverse events. Ten of the 34 adverse events were considered treatment-related with the most common adverse reaction being application site pruritus (8 events in 8 subjects). There were no severe AE's.

- Pregnancy: One subject (844) had a positive urine pregnancy test at study exit. The outcome of the pregnancy was unremarkable.

Reviewer's assessment: Under test conditions of near maximal stress, OTG has no evidence of cumulative irritation.

10.1.3 Study OG05004

Study Title: "A repeat insult sensitization test of active and placebo topically applied oxybutynin gel in healthy volunteers"

Study period: January 2006 - March 2006

Objective: To evaluate the incidence of contact sensitization following repetitive applications of active and placebo oxybutynin gel

Study design and conduct: This was a single-center, single-blind, repeat insult patch test of active and placebo oxybutynin gel. Each subject received both test materials (0.5 g OTG 10% and 0.5 g placebo gel) applied to contralateral shoulders and covered with a gauze pad. The assignment of the test gels was randomized within each subject. The test materials were applied 3 times a week for 3 consecutive weeks (induction phase). A trained skin evaluator blinded to the application sites of the test and control systems conducted skin evaluations within 5 minutes of gauze removal and prior to the next gel application. After the induction phase, a rest period of 2 weeks was followed by a single 48-hour challenge application with skin evaluations at 5 minutes, 24 hours, 48 hours, and 72 hours after gauze removal. Safety evaluations consisted of monitoring of adverse events.

Reviewer's comment: Reviewer's comment*: According to the sponsor, the study design was the "Jordan-King modification of the Draize Procedure that is the standard study design for human repeated insult patch test." The study investigates the sensitization potential of OTG 10% under modified conditions of maximal stress. Rather than using the occlusive patch, the study used an open patch method to better simulate conditions of therapeutic use. This modification is acceptable. Otherwise, the remainder of the study design and conduct of OG05004 are consistent with the Agency's recommendations for a Skin*

Sensitization Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).

Summary of study schedule:
Induction Period:

Visit	INDUCTION PERIOD											
	1		2	3	4	5	6	7	8	9	10	Make up[1]
Study Day	Up to -28	1	3	5	8	10	12	15	17	19	22	24
Obtain Consent	X[2]											
Inc/Exc Criteria	X[2]											
Medical History	X[2]											
Vital Signs and Skin Evaluation		X										
Pregnancy Test (women of childbearing potential)		X										
Test Article Application		X	X	X	X	X	X	X	X	X	X[1]	
Pad Removal			X	X	X	X	X	X	X	X	X	X[1]
Skin Reaction Evaluation			X	X	X	X	X	X	X	X	X	X[1]
Assess AE's		X	X	X	X	X	X	X	X	X	X	X[1]
Deviation Documentation		X	X	X	X	X	X	X	X	X	X	X[1]
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X[1]

[1] Procedures or visit only required for subjects missing one visit.
[2] Procedures may have been conducted on day 1.

Challenge Phase:

Visit	REST PHASE	CHALLENGE PHASE				
	none	11	12	13	14	15
Study Day	22-35	36	38	39	40	41
Pregnancy Test (women of childbearing potential)		X				X
Test Article Application		X				
Pad Removal			X			
Skin Reaction Evaluation			X	X	X	X
Assess AE's		X[1]	X	X	X	X
Deviation Documentation		X	X	X	X	X
Concomitant Medication		X[1]	X	X	X	X
Termination Sheet						X[2]

[1] Adverse events experienced and use of concomitant medication during the rest phase were recorded.
[2] Completed at the final visit or at any time the subject was prematurely discontinued.

<u>Eligibility Criteria</u>:
Inclusion:

- Male or female, 18 to 65 years old
- Using effective contraception or of non-childbearing potential (women only)
- Non-pregnant (negative pregnancy test on Day 1)
- Healthy
- Provide informed consent

Exclusion:

- Pregnant or lactating
- Known or suspected hypersensitivities to oxybutynin or other anticholinergic agents or any component of the gel formulation
- History of narrow angle glaucoma, urinary or gastric retention, or significant sensitivity or allergy to adhesive bandages, tapes, etc.
- Hair, tattoos, pigmentation, scars, moles or other conditions to the area to be treated that may interfere with the application, tolerability, or post-application evaluations
- Clinically significant skin conditions (psoriasis, eczema, atopic dermatitis, and active cancer) within 1 year
- Participation in a patch test or soap chamber test within 4 weeks of the study
- Participation in a clinical trial or receipt of an investigation medication within 1 month of the study
- Routine use of anti-inflammatory, immunosuppressive or antihistamine medications
- Current use of allergy injections
- Use of systemic or topical anti-inflammatories or antihistamines within 72 hours of study enrollment, (subjects taking 81mg of aspirin for cardiovascular preventative were allowed to participate)
- Use of systemic or topical corticosteroids within 3 weeks of study enrollment
- Severe asthma, active immunologic disorders, insulin dependent diabetes, clinically significant chronic illness which could have placed the subject at increased risk during participation or resulted in an inappropriate dermal response during the study
- Alcohol or drug abuse within 1 year of the study
- Inability to provide written informed consent or judged by the investigator to be unsuitable for any reason

Evaluation variables:
The primary study variable was the contact sensitization potential of 10% OTG and placebo gel. The following scale was used to evaluate skin reactions during the induction period and challenge phase. A score was assigned when a clinically significant skin reaction was noted or ≥ 25% of the test site showed a skin response.

Scoring system for skin response:

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Skin Responses – numeric grades:

0	No visible reaction and/or erythema
+	Slight, confluent or patchy erythema
1	Mild reaction – macular erythema (faint, but definite pink)
2	Moderate reaction – macular erythema (definite redness, similar to a sunburn)
3	Strong to severe reaction – macular erythema (very intense redness)

Skin Responses – letter grades:

E	Edema – swelling, spongy feeling when palpated
P	Papule – red, solid, pinpoint elevation
V	Vesicle – small elevation containing fluid
B	Bulla reaction – fluid-filled lesion (blister)
S	Spreading – evidence of the reaction beyond the application area
W	Weeping – result of a vesicular or bulla reaction – serous exudate
I	Induration – solid, elevated, hardened, thickened skin

Skin Responses – additional observation grade:

g	Glazing
y	Peeling
c	Scab, dried film of serous exudate of vesicular or bulla reaction
d	Hyperpigmentation (reddish-brown discoloration of test site)
h	Hypopigmentation (loss of visible pigmentation at test site)
f	Fissuring – grooves in the superficial layers of the skin

Reviewer's comment*: According to the sponsor, the dermal scoring system is the standard measure for scoring in sensitization studies.*

Statistical considerations:

Sample size: The sponsor planned to enroll 240 subjects with a goal of 200 completers and a minimum of 80 subjects of each gender. This sample size is standard for a sensitization study.

Analysis populations: Clinical analysis and data tabulation for the skin sensitization evaluations was performed using the Per Protocol (PP) population, which included all randomized subjects who completed the study (received 9 induction applications each of test and control gels and whose challenge sites were evaluated at least twice (5 minutes and 24 hours after the removal of the challenge gauze pad). All other analyses were performed using the Safety population, which included all randomized subjects who received at least one dose of study drug.

Skin sensitization analysis: The interpretation of data was based on the pattern of reactivity of the test article during induction phase compared to the severity and persistence of the reaction(s) observed at Challenge. Increased reactivity noted during the first week of induction to test articles considered non-irritating or minimally irritating generally indicated a pre-sensitized condition. Comparable reactivity during the third week, if it appeared suddenly, was suggestive of the initiation of sensitization. Irritation generally developed more gradually and was resolved with a comparable sequence after test article removal. A narrative description of each reaction in the challenge phase was provided with the investigator's opinion as to whether such reactions were indicative of contact sensitization or irritation.

***Reviewer's comment**: Contact dermatitis falls into 2 main categories: irritant and hypersensitivity. Both involve inflammatory processes and can have similar clinical characteristics of erythema, induration, scaling, and vesiculation in areas of direct contact with the chemical. The pattern of response is important to differentiating whether a skin reaction is of irritation or allergic nature. The inflammatory response to contact irritants is gradual and proportional to the dose. Allergic contact dermatitis is a delayed, T-cell mediated hypersensitivity reaction. The memory T-cells are generated over a 1-3 week period. Upon re-exposure to the allergen, the inflammatory response is immediate and proportionally much larger than the dose.*

Subject Disposition:
A total of 225 subjects were enrolled and treated, and 200 subjects completed the study. The PP population included 200 subjects and the Safety population included 225 subjects. Twenty-five subjects withdrew prematurely: 6 due to adverse events, 5 due to protocol violation, 9 due to refusal/inability to participate further, and 5 were lost to follow-up. Although there were no major protocol violations, there were 469 minor violations. The most common minor violation included skin evaluations not conducted with in the allotted time periods or not conducted (n = 245 or 50%).

***Reviewer's comment**: A review of the line listing of protocol deviations by subject (study report, Appendix 16.2.23) showed that 6 patients had at least one missing evaluation or had an evaluation but a score was not recorded. Given the number of skin evaluations for each subject, this reviewer does not anticipate that these missing data would significantly alter the study findings.*

Demographics and baseline characteristics::
Subjects were primarily non-Hispanic (91%) White (87%) men (39%) and women (61%) with an average age of 42 years. The demographics were similar between the PP and Safety populations.

Skin sensitization results:
One subject experienced contact sensitization to the active gel (0.5%). Subject 1087 had mild erythema and papules at each of the challenge evaluations of the active OTG application site. Re-challenge was performed on Subject 1087 who again experienced mild erythema with papules on the OTG application site at the 5-minute, 24-hour, 48-hour, and 72-hour after the removal of the rechallenge gauze pad.

***Reviewer's comment**: This reviewer reviewed the line listing of dermatologic evaluations of all subjects. Subject 1020 had +P score (slight, confluent or patchy erythema; red, solid, pinpoint papules) after the 8th and 9th but did not have any skin reaction during the challenge phase. No other subjects had any significant trend of skin reactions in the Induction period and Challenge Phase.*

Skin tolerability results*:* The findings of skin tolerability in the Challenge phase and Induction period are summarized in Table 1 and Table 2.

Table 1: Dermal Evaluation Scores during Challenge Phase

Time after gauze removal	**5 Minutes**		**24 hours**		**48 hours**		**72 hours**	
Skin irritation Score*	Placebo N=201	OTG N=201	Placebo N=201	OTG N=201	Placebo N=200	OTG N=200	Placebo N=200	Gel N=200
0	190	187	198	193	198	199	197	195
+	10	13	3	5	1	0	1	2
1	1	1	0	3	1	1	0	1
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
Not scored (NS)	0	0	0	0	0	0	2	2

Source: Study report, tables 11.4.1.1-2 and 11.4.1.1-1, p. 23-24

*0=no visible reaction and/or erythema; +=slight, confluent or patchy erythema; 1=mild reaction, macular erythema (faint but pink); 2=moderate reaction macular erythema (redness similar to sunburn); 3=strong to severe reaction, macular erythema (very intense redness)

Table 2: Dermal Evaluation Scores during Induction Period

Application #	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
N=201	P*	O*	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O
+	8	9	14	17	13	13	9	9	8	8	2	4	5	5	5	6	10	8
1	0	2	1	4	1	7	1	2	0	0	0	0	0	0	0	1	1	2
2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NS	0	0	1	1	1	0	0	1	0	0	0	0	1	1	0	0	2	1

*P=placebo; O=OTG
Source: Study report, tables 11.4.1.2-1 and 11.4.2.2-2, p. 25-26

***Reviewer's comment**: The skin tolerability assessment was based primarily on erythema changes at the application site. There were no moderate or severe reactions in the OTG group. During the Induction period, 2-8% of OTG application sites showed slight, confluent or patchy erythema (+) compared to 1-6% of placebo application sites. During the same period, 0-2% of OTG application sites showed mild reaction, macular erythema (score = 1) compared to 0-0.5% of placebo gel sites.*

Safety analysis:

- *Extent of exposure*: Two hundred and twenty five (225) subjects were enrolled in the study and received at least one dose of gel application. Two hundred and one (201) subjects received all 9 Induction applications and Challenge applications, and one subject received one re-challenge application. Twenty five (25) subjects were exposed to between 1 and 10 applications before discontinuing their participation in the study.

- *Adverse events*: 91 subjects (40.4%) reported a total of 148 adverse events. One death related to alcoholism and unrelated to treatment occurred (subject 1039). No other SAE was reported. Of the 25 subjects who discontinued prematurely, 6 withdrew because of an adverse event (2 subjects experienced diarrhea, one subject each experienced blurred vision, urinary tract infection, tape irritation at application sites, and death from complications of alcoholism). The most common adverse events were related to the application sites. Fifty-three (53) subjects reported 103 application site adverse events. Seven subjects reported 16 application site adverse

reactions (application site irritation, pruritus, and warmth). The distribution of the application site adverse reactions was similar between the placebo and active gel. Other adverse reactions included dry mouth (1), diarrhea (3), dry throat (1), abdominal cramps (1), blurred vision (1), and dizziness (1).

- *Pregnancy*: None

Reviewer's comment*: A review of the line listing of all adverse events was conducted. No unexpected AE's occurred.*

Reviewer's assessment: Under test conditions, one subject (0.5%) was sensitized to 0.5 g OTG 10% and none was sensitized to placebo gel.

10.1.4 Study OG06007

Study Title: "An evaluation of the person-to-person transference and absorption potential of oxybutynin following application of oxybutynin topical gel to healthy volunteers"

Study period: March 2007 – April 2007

Objective: To determine the potential of topically applied oxybutynin gel to be transferred between treated and untreated subjects by direct physical contact at the application site

Study design and conduct: This was a single-center, open-label, randomized, single dose, parallel group study evaluating the potential of person-to-person transference of 10% OTG. Subjects were randomized to receive one dose of 1 g 10% OTG applied to the abdomen (treated) or no treatment (untreated). The treated subjects were further randomized to cover the application site with clothing or remained unclothed during the physical contact with untreated subjects. At one hour post-application, the treated and untreated subjects engaged in direct physical contact (abdomen-to-abdomen) at the application site for 15 minutes. Blood samples for oxybutynin and N-desethyloxybutynin PK parameters were drawn from untreated subjects at 0 (before contact), 2, 4, 8, 12, 36 and 48 hours after the physical contact. Treated subjects provided one blood sample drawn 3 hours post-application to verify dosing. Adverse events were monitored.

Eligibility Criteria:
Inclusion:

- In general good health and aged 18 to 45 years
- Using a medically accepted contraceptive (women of childbearing potential only)
- BMI of 18-30 and weight ≥ 50 kg and ≤ 90 kg
- Provide written informed consent

Exclusion:

- Significant findings on physical exam
- Current acute or chronic medical therapy
- Clinically significant laboratory or ECG findings
- History of narrow angle glaucoma or urinary or gastric retention
- Pregnant or lactating
- Recent history (within last year) or current alcohol or drug abuse

- Tobacco use within past 6 months
- Dermatological diseases, skin damage or blemishes that may affect tolerability of gel or its assessment
- Blood donation within past 12 weeks
- Hypersensitivities, allergies, or contraindications to any component of the gel formulation
- Inability to comply with treatment schedule
- Participation in an investigational drug study within 30 days prior to the screening visit
- Excessive hair growth on the abdomen which would interfere with the application of the gel
- Judged by investigator to be unsuitable for enrollment

Study Variables:
The primary variables were plasma oxybutynin concentrations and the derived PK parameters ($AUC_{[0-48]}$, Cmax, Tmax) in the untreated subjects. Safety variables were adverse events, skin tolerability, and vital signs.

Statistical considerations:
All statistical analyses were descriptive in nature. The PK analyses were performed using the Evaluable population, which included all untreated subjects who completed the study, provided all plasma concentration data from each sampling time period, and who did not have any major protocol deviations. The Safety population included all treated subjects who received at least one dose of study drug and untreated subjects who participated in the physical contact with treated subjects.

Subject Disposition:
Fifty-two (52) subjects were enrolled in the study and 52 completed the study. The Evaluable population included 25 subjects; one untreated subject (1509-b) did not provide blood for all sample draws and was excluded. A review of PK findings of subject 1509-b, who participated in the skin-to-clothing contact regimen, indicated that the subject had not detectable oxybutynin plasma levels at any of the sampled time points. The Safety population included 52 subjects. No important protocol violation or the use of concomitant medications occurred that were felt to affect the study results.

Demographics and baseline characteristics: The Safety population consisted of 25 male and 27 female subjects with a mean age of 25 years (range 18-44 years). The Evaluable population was comprised of 11 male and 14 female subjects. All subjects were healthy and met all the eligibility criteria.

Person-to person transference results: All untreated subjects had measurable oxybutynin levels after direct skin-to-skin contact with treated subjects at the application site. Oxybutynin levels were detectable at the first blood draw post-contact (2 hours) and continued to be detectable 48 hours post-contact. The mean Cmax of 0.94 ng/mL occurred at approximately 18 hours after the skin-to-skin contact. Although drug transference occurred in both male and female untreated subjects, female subjects tend to absorb more drug and had higher mean Cmax oxybutynin concentrations than males. The PK findings are summarized in Table 1.

Table 1: Oxybutynin PK Parameters Following Skin-to-Skin Contact

PK Parameter	Statistic	Female subjects N=7	Male subjects N=6	All N=12
AUC $_{[0-48]}$ (ng.hr/mL)	Mean (SD)	37.7 (29.0)	18.7 (11.1)	29.8 (24.5)
	Min, Max	11.0, 85.7	9.4, 32.5	9.4, 85.7
Cmax (ng/mL)	Mean (SD)	1.14 (0.9)	0.7 (0.5)	0.94 (0.7)
	Min, Max	0.4, 2.3	0.3, 1.2	0.3, 2.3
Tmax (hr)	Mean (SD)	15.7 (8.1)	19.5	17.3
	Min, Max	8.3, 24.3	12.3, 24.3	8.3, 24.3

Source: Study report, Table 11-2, p. 25

***Reviewer's comment**: In other single-dose PK studies with 1 g 10% OTG; female subjects had slightly higher Cmax and AUC than male subjects. The differences appeared to be too small to be clinically significant.*

As a comparison, in Study OG04007 where healthy subjects received one dose of 1 g 10% OTG and PK parameters were evaluated for 144 hours post-application, the mean Cmax (ng/mL) was 4.7 ng/mL and the mean AUC (0-144) was 220 ng/mL. The median Tmax was approximately 20 hour post-application.

Twelve of the 14 untreated subjects participating in the skin-to-clothing contact (treated subjects covered the application site with clothing) had no detectable plasma oxybutynin levels at any of the sampled time points. Two subjects had measurable oxybutynin plasma levels starting at 8 hours post-contact. Both of these subjects were females. For subject 1508-b, Cmax was 0.07 ng/mL and AUC (0-48 h) was 1.86 ng/mL. For subject 1514-b, Cmax was 0.1 ng/mL and AUC (0-48 h) was 1.57 ng.h/mL

***Reviewer's comment**: A review of PK parameters of individual subjects was conducted.*

- *All untreated subjects participating in the skin-to-skin contact had detectable plasma oxybutynin levels indicating 100% potential for systemic absorption of OTG.*
- *Two untreated patients participating in the skin-to-clothing contact had detectable plasma oxybutynin levels. For subject 1508-b, Cmax occurred at 8 hours after contact. At the 48 hour time point, the plasma oxybutynin concentration was 0.05 ng/mL. For subject 1514-b, Cmax occurred at 8 hours after contact. Oxybutynin plasma levels were no longer detectable after 24 hours post-contact. The plasma oxybutynin levels of the treated partners of these 2 untreated subjects were similar to those of other treated subjects.*
- *The oxybutynin exposure levels observed in the 2 untreated subjects with detectable plasma oxybutynin were minimal and should not pose a significant safety concern except in patients with hypersensitivity to OTG or to oxybutynin. Covering the application site with clothing provided sufficient protection from person-to-person transference of OTG.*

Safety: Twenty six (26) subjects received one dose of 1 g 10% OTG, and 14 untreated partners were exposed to oxybutynin to a variable extent through physical contact with the treated subjects at the application site. One subject (1512-b) who was the untreated partner participating in the clothing-to-skin contact regimen reported one unrelated adverse event of mild myalgia. No other adverse events were reported.

Reviewer's assessment: 10% OTG is transferable from a treated person to an untreated partner through direct skin-to-skin contact at the application site. This risk can be sufficiently minimized by covering the application site with clothing.

10.1.5 Study OG06001

Study Title: "Plasma oxybutynin and N-desethyloxybutynin concentrations following application of 1 g 10% oxybutynin topical gel when co-administered with sunscreen at the same application site"

Study period: April 2006 – May 2006

Objective: To evaluate the effect of sunscreen on the rate and extent of absorption of oxybutynin when sunscreen was applied before and after applications of OTG. Secondary objectives included the evaluating of the effect of co-administration of OTG and sunscreen on the metabolism of oxybutynin, local skin tolerability, and adverse events.

Study design and conduct: This was a single center, 3-period, open-label, randomized crossover study of single dose applications of 1 g 10% OTG. Subjects received 3 treatments (OTG application alone, OTG application preceded by sunscreen application, OTG application followed by sunscreen application) in a randomized sequence with each subject receiving each study treatment once. There was a minimum 14-day washout between each treatment. During the treatment period where the OTG and sunscreen were both administered, the products were applied to the same site (abdomen) 30 minutes apart. Blood samples were collected for plasma oxybutynin and N-desethyloxybutynin levels prior to OTG application and 2, 6, 12, 16, 20, 24, 28, 48, and 72 hours following OTG application. Safety evaluations included monitoring of adverse events and skin tolerability (erythema scores) assessment. See Study Schedule.

Study Schedule:

	Days -14 to -2	Days -1,14,28	Days 1,15, 29	Days 2,16,30	Days 3,15,31	Days 4,18,32	Day 32/ ET
Informed consent	X						
Inclusion / exclusion	X						
Demographic Data	X						
Body Weight/Height	X						
Medical History	X						
Current Illness / Meds	X	X					
Vital Signs	X						X
Physical Examination	X						
ECG	X						
Clinical Lab Tests	X						
Urinalysis	X						
Drug Screen	X	X					
Pregnancy Test	X	X					X
Gel/Sunscreen Application			X				
Blood Samples			X	X	X	X	
Skin Tolerability			X	X			
Adverse Event Query			X	X	X	X	X
Confinement in Clinic			X	X			
Exit Study							X

Source: Study report, Table 9-2, p. 16

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***Reviewer's comment**: The sunscreen used in the study was a water-based, oil-free SPF 15 product. The dose of sunscreen used was 800 mg per each application based on the FDA guidance specification of application of 2 mg/cm2 of application surface area in studies evaluating sunscreen products (Over-the-Counter Drug Products Monograph on Sunscreens (Final Version). US Food and Drug Administration, Federal Register 1999: 64: 27666-27963).*

Eligibility Criteria:
Inclusion:

- In general good health and aged 18 to 45 years
- Using a medically accepted contraceptive (women of childbearing potential only)
- BMI of 18-30 and weight ≥ 50 kg and ≤ 90 kg
- Provide written informed consent

Exclusion:

- Significant findings on physical exam
- Current acute or chronic medical therapy
- Clinically significant laboratory or ECG findings
- History of narrow angle glaucoma or urinary or gastric retention
- Pregnant or lactating
- Recent history (within last year) or current alcohol or drug abuse
- Tobacco use within past 6 months
- Dermatological diseases, skin damage or blemishes that may affect tolerability of gel or its assessment
- Blood donation within past 12 weeks
- Hypersensitivities, allergies, or contraindications to any component of the gel formulation
- Inability to comply with treatment schedule
- Participation in an investigational drug study within 30 days prior to the screening visit
- Excessive hair growth on the abdomen which would interfere with the application of the gel
- Judged by investigator to be unsuitable for enrollment

Study Variables:
The primary variables were the PK parameters ($AUC_{[0-24]}$, $AUC_{[0-72]}$, Cmax, Tmax) derived from plasma oxybutynin and DEO concentrations. Safety variables included adverse events, skin tolerability, and vital signs.

Statistical considerations:
All statistical analyses were descriptive in nature. PK analyses were analyzed using the Evaluable population, which included all subjects who completed all 3 treatment periods and who did not have any major protocol violations. Safety analyses were analyzed using the Safety population, which included all subjects who received at least one dose of study drug.

Subject disposition: 16 subjects were enrolled and 14 subjects completed the study. One subject (1210) withdrew consent prior to Treatment Period 3, and one subject (1204) was withdrawn during Period 3 due to use of excluded medication. There were no major protocol violations.

Demographic and baseline characteristics: The Safety population comprised of 16 subjects (8 males, 8 females) with a mean age of 25.9 years (range 19 to 45 years). The Evaluable population consisted of 14 subjects (6 males, 8 females). All subjects were Caucasian and met the eligibility criteria.

Plasma oxybutynin and DEO concentrations and PK with OTG and sunscreen applications

The PK findings are summarized in Table 1.

Table 1: Oxybutynin PK Parameters by Treatment Regimen

PK Parameter	Statistic	OTG alone	Sunscreen/OTG	OTG/Sunscreen
AUC (0-72) (ng.h/mL)	Mean (SD)	84.5 (48.6)	91.2 (55.5)	83.6 (41.4)
	Min, Max	17.6, 167.0	26.2, 207.9	26.8, 166.2
Cmax (ng/mL)	Mean (SD)	2.7 (1.7)	3.01 (2.0)	3.02 (1.8)
	Min, Max	0.54, 5.5	0.7, 7.4	0.8, 6.4
Tmax (h)	Mean (SD)	23.4 (4.9)	25.7 (4.1)	23.7 (5.5)
	Min, Max	12, 28.0	20, 36	12, 36
DEO:OXY AUC $_{(0\text{-}72\ h)}$		0.82	0.86	0.78

Source: Study report, Table 11-2, p. 28

***Reviewer's comment**: Based on mean values, compared to OTG alone, applying sunscreen 30 minutes prior to OTG application resulted in a slight increase in AUC, Cmax, and Tmax. Applying OTG 30 minutes prior to applying sunscreen resulted in a slight increase in Cmax. These differences are not likely to result in clinically meaningful differences in safety.*

Safety:

- *Extent of exposure*: 16 subjects received at least one dose of study drug, and 14 subjects received all 3 doses of 1 g 10% OTG. Two subjects withdrew after receiving 2 applications. Subject 1210 did not return to the clinical for the third dosing period, and subject 1204 withdrew before dosing in Period 3 due to exclusionary concomitant medication use.

- Adverse events: Two subjects reported 2 adverse events. One subject reported a mild headache and another subject experienced allergic contact dermatitis after exposure to poison ivy. Neither one of these AE's were treatment-related.

- Skin tolerability: No subject experienced any erythema after any OTG application with or without sunscreen, and no subject reported any application site reaction.

Reviewer's assessment: Sunscreen administered 30 minutes before or after OTG application did not affect the PK or metabolism of OTG 10%.

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CLINICAL REVIEW

Application Type	NDA
Submission Number	22-204
Submission Code	N
Letter Date	March 26, 2008
Stamp Date	March 27, 2008
PDUFA Goal Date	January 27, 2009
Reviewer Name	Christine P. Nguyen, M.D.
Review Completion Date	January 14, 2009
Established Name	Oxybutynin chloride
(Proposed) Trade Name	Gelnique
Therapeutic Class	Antimuscarinic
Applicant	Watson Laboratories, Inc.
Priority Designation	S
Formulation	Transdermal gel
Dosing Regimen	1 g once daily (100 mg oxybutynin)
Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Intended Population	Adults with overactive bladder
Related IND's/NDA's	67,126 (Oxybutynin Transdermal Gel) 50,489 (Oxytrol TDS) NDA 21-351 (Oxytrol TDS)

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1 EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

From a clinical perspective, Oxybutynin Transdermal Gel 10% 1 gram applied once daily should be approved for the indication of "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency" in adults with overactive bladder, pending the Office of Compliance's recommendation regarding the acceptability of the manufacturing sites.

This recommendation is based on the demonstration of "substantial evidence" of effectiveness in improving symptoms of overactive bladder in the target population and an acceptable safety profile.

1.2 RECOMMENDATION ON POSTMARKETING ACTIONS

No new safety concerns have been identified which require actions other than routine postmarketing surveillance.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

Oxybutynin has been approved for the symptomatic treatment of overactive bladder (OAB) since 1975. It is a tertiary amine that is thought to exert its therapeutic effects by muscarinic receptor blockade of the M3 receptor subtypes that predominate in the bladder and are thought to mediate detrusor contractibility. Oxybutynin exists commercially as a racemic mixture of R- and S-enantiomers (R-OXY, S-OXY). In-vivo and animal studies have been conducted with conflicting results regarding whether the pharmacological effects and anticholinergic activities of racemic oxybutynin are attributable primarily to the R or S isomer.[1,2]

The continued use of and patient compliance with oxybutynin treatment have been limited by anticholinergic side effects, such as dry mouth and constipation. The sponsor developed a transdermal matrix formulation of oxybutynin (Oxytrol Transdermal System, or Oxytrol TDS) in an attempt to improve the tolerability profile of oxybutynin. Unlike oral administration, transdermal delivery of oxybutynin avoids the first-pass metabolism resulting in decreased conversion of oxybutynin to N-desethyloxybutynin (DEO), a major active metabolite thought to contribute significantly to the anticholinergic side effects of oxybutynin. The transdermal delivery system is thought to result in an improved tolerability profile and better patient compliance. The primary disadvantage of the oxybutynin transdermal matrix delivery system, however, is application site reactions. In controlled clinical trials for Oxytrol TDS, approximately 16-21% of patients reported application site reactions, and approximately 10% of patients discontinued therapy because of these reactions. Oxytrol TDS (3.9 mg/day), an occlusive matrix-type transdermal patch, was approved for the symptomatic treatment of overactive bladder in 2003.

The sponsor developed oxybutynin transdermal gel (OTG) as a second generation product for Oxytrol TDS. An un-occluded gel system was considered to have better skin tolerability than the occlusive Oxytrol TDS. The clinical development plan focused on defining an OTG formulation and dose that would provide blood levels and exposures of oxybutynin and DEO similar to Oxytrol TDS (3.9 mg/day). The proposed dose is one sachet containing 1 g of 10% oxybutynin gel once daily with no specific dose adjustments for specific populations. The data to support the safety and efficacy of 1 g OTG 10% came from one large, multicenter, randomized, double-blind, and parallel group study of 12 weeks duration

followed by a 14-week open-label extension in 789 adult men and women with overactive bladder (Study OG05009).

The sponsor seeks approval of 1 g 10% OTG for the "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." OTG has not been approved for marketing in any country.

***Reviewer's comment**: During the teleconference held on November 2, 2005, the Division stated that a single safety and efficacy study with $p \leq 0.05$ could be adequate to support approval of an NDA, provided that confirmatory evidence exists, no conflicting evidence exits, and the PK data are sufficiently supportive. In the clinical development of OTG, clinical efficacy was evaluated only in one clinical study (OG05009) using one drug dose.*

1.3.2 Efficacy

The **primary efficacy endpoint** in Study OG05009 was change from baseline to Endpoint (Week 12, LOCF) in the number of urinary incontinence episodes per day recorded in the 3-day urinary diary in the 12-week double-blind study period. Currently, this endpoint is an accepted primary endpoint in phase 3 clinical trials evaluating treatment of symptomatic OAB. Compared to placebo, OTG treatment resulted in statistically significant improvement in the number of daily urinary incontinence episodes. At baseline, the mean (5.4) and median (4.7) numbers of urinary incontinence episodes per day were identical for both treatment groups. At Endpoint (Week 12, LOCF), the mean change from baseline in the number of daily urinary incontinence episodes was -3.0 for the OTG treatment group and -2.5 for the placebo group. The mean difference in the primary endpoint between the OTG and placebo groups was -0.5 episodes per day (95% CI: -0.14, -0.87), and this difference was statistically significant ($p < 0.0001$). The study was powered to detect a difference of -0.52 incontinence episodes per day between the 2 study groups and this anticipated mean difference was achieved at Endpoint. Statistically significant improvement in urinary incontinence associated with OTG treatment was observed starting at Week 4 and maintained to Week 12. See Table 1.

Table 1: Change from Baseline Incontinence Episodes per Day (mITT)

Visit	Statistics	Placebo	OTG
Baseline	N Mean (SD) Median	400 5.4 (3.3) 4.7	389 5.4 (3.3) 4.7
Week 1 (OC)	N Mean (SD) Median p-value*	390 -1.8 (2.6) -1.3	384 -2.0 (2.4) -1.7 0.18
Week 4 (OC)	N Mean (SD) Median p-value*	374 -2.3 (2.9) -2.0	366 -2.7 (2.6) -2.3 **0.0004**
Week 8 (OC)	N Mean (SD) Median p-value*	359 -2.5 (2.9) -2.0	354 -3.0 (2.6) -2.7 **0.0002**
Week 12 (OC)	N Mean (SD) Median p-value*	358 -2.6 (3.1) -2.3	348 -3.0 (2.8) -2.7 **0.0004**
Week 12 (LOCF)	N Mean (SD) Median p-value*	400 **-2.5** (3.1) -2.0	389 **-3.0** (2.7) -2.7 **<0.0001**

*Versus Placebo comparing least squares adjusted means
Source: Module 2.7.3, Summary of Clinical Efficacy, p. 15-16

The 2 major **secondary endpoints** were changes from baseline in daily urinary frequency and in the average volume per void.

Daily urinary frequency: At baseline, the mean (OTG: 12.4, placebo: 12.2) and median (OTG: 11.7, placebo: 11.3) daily urinary frequency were similar between the OTG and placebo groups. Compared to placebo, OTG treatment resulted in statistically significant improvement in daily urinary frequency at Endpoint (p=0.0017). At Endpoint, the mean change from baseline in daily urinary frequency was -2.7 episodes for the OTG group compared to -1.7 episodes for the placebo group.

Average urine volume per void: At baseline, the mean (OTG: 163 mL, placebo: 168 mL) and median (160 mL for both treatment groups) average urine volume per void were similar between the OTG and placebo groups. Compared to placebo, OTG treatment resulted in a statistically significant increase in the average urine volume per void at Endpoint (p=0.0018). At Endpoint, the mean change from baseline in the average urine volume per void was +21.0 mL for the OTG group compared to +3.8 mL for the placebo group.

The improvement in the number of daily urinary incontinence episodes with OTG treatment was clinically and statistically meaningful. The improvements in daily urinary frequency and average urine volume per void were statistically significant and consistent with the primary result. Although there is no

comparative efficacy trial of the two transdermal oxybutynin products, the improvements in the key efficacy endpoints appear to be comparable between 1 g 10% OTG and Oxytrol TDS (3.9 mg/day).

1.3.3 Safety

Safety data were based on a total of 1033 subjects who received at least one dose of OTG. These subjects were enrolled in 14 completed trials, 13 of which were conducted in the U.S. The 1033 subjects included 496 OAB patients in the integrated phase 3 study (double blind and open-label), 216 healthy subjects in the integrated phase 1 studies, and 296 healthy subjects in the non-integrated phase 1 studies. A total of 433 patients (346 from double-blind and 87 from open-label phase 3 study) were exposed to ≥ 12 weeks of treatment and 71 patients completed 26 weeks of treatment. The patient population in the phase 3 study was similar to the target population. Overall, this is an adequate safety database for oxybutynin.

Compared to placebo, OTG treatment was associated with an excess of treatment-emergent adverse events in the placebo-controlled phase 3 study (57% versus 48%). More patients in the OTG group than placebo withdrew due to an adverse event (4.9% versus 3.3%) or experienced a treatment-related adverse event (19% versus 11%). Most of the reported adverse events were known anticholinergic side effects and dermatologic application site reactions. The most common adverse events were dry mouth, urinary tract infection, dizziness, application site pruritus, and fatigue. The most common treatment-related adverse events, or adverse reactions, were dry mouth (OTG: 6.9%, placebo: 2.8%) and application site reactions (OTG: 5.4%, placebo: 1%). Compared to placebo, OTG treatment was not associated with an excess of deaths, non-fatal serious adverse events, neurologic, cardiac, hepatic, hematologic, or renal toxicity. No new or unexpected adverse events or reactions were noted in the phase 3 open-label extension or in the phase 1 studies. During the clinical development of OTG, the following 4 safety issues were specifically addressed:

1. Skin tolerability: Skin tolerability was assessed in the 11 integrated safety studies, including the phase 3 study. Skin tolerability was systematically assessed by visually inspecting the gel application area for erythema changes at variable time points after study drug application. Overall, the proportion (< 5%) and severity (mild to moderate) of erythema changes in the OTG group were not significantly greater the placebo group. The risk of developing erythema at the application site did not increase significantly with longer duration of OTG use. Although there is no direct comparison between OTG and Oxytrol TDS, available clinical evidence suggests that skin tolerability of OTG may be better than Oxytrol TDS.

   During the entire phase 3 study (double-blind and open-label), application site adverse reactions were reported by approximately 6% of patients on active treatment compared to 1% of placebo patients. Approximately 2% of OTG-exposed patients discontinued therapy because of application site reactions compared to < 1% of patients on placebo. The incidences of application skin reactions and treatment discontinuation due to an application site reaction increased slightly with longer duration of OTG use.

2. Dermatologic safety: The potential of OTG for skin irritation and skin sensitization was evaluated in 2 placebo-controlled dermatoxicity studies. Results from a 21-day cumulative skin irritation study indicated that OTG is not an experimental skin irritant. In the skin sensitization study, one subject (0.5%) experienced mild contact sensitization to OTG.

3. Person-to-person transference: In a PK transference study, direct physical contact at the OTG application site leads to dermal transfer and systemic absorption of oxybutynin to the untreated

partner. This skin-to-skin transference, however, can be significantly mitigated by covering the application site with clothing.

4. Co-administration of OTG with sunscreen: The absorption and metabolism of oxybutynin were not affected by the application of sunscreen 30 minutes before or after OTG gel application.

Overall, the safety findings of OTG were expected of an oxybutynin product. Although data directly comparing the skin safety of Oxytrol TDS and OTG were not submitted with this application, data available for these 2 products suggest improved skin tolerability with OTG compared to Oxytrol TDS.

1.3.4 Dosing Regimen and Administration

The 1 g 10% OTG dose was selected based on results from studies OG04007 and OG06005. Pharmacokinetic modeling of single doses of 1 g and 3 g 10% OTG predicted that the 1 g dose would most closely match the delivery of Oxytrol TDS (3.9 mg/day). This prediction was confirmed by a direct steady state PK comparison of the 2 products where 1 g 10% OTG produced oxybutynin exposure and plasma drug concentrations similar to those of Oxytrol TDS.

***Reviewer's comment**: The dose selection was based on PK results and not clinical efficacy findings. At steady state, DEO concentration and exposure (Cavg, AUC) was approximately 25% less after OTG dosing than Oxytrol dosing. Although DEO is a pharmacologically active metabolite, the exposure-response relationship of DEO is not well-characterized. According to the clinical pharmacology reviewer, the OXY + DEO concentration and exposure were similar between 1 g 10% OTG and Oxytrol TDS 3.9 mg/day.*

1.3.5 Drug-Drug Interactions

No drug-drug interaction studies or data were submitted for OTG. No formal drug-drug interaction studies have been conducted with Oxytrol TDS. For OTG, the sponsor proposes the same general drug-drug interaction language found in the Oxytrol TDS label, which cautions against the concomitant use of OTG with other anticholinergic products and states the unknown effect of concomitant use of cytochrome P450 enzyme inhibitors.

***Reviewer's comment:** According to the Ditropan label, mean oxybutynin plasma levels increased 3- to 4-fold when Ditropan was administered with a potent CYP3A4 inhibitor (ketoconazole). This drug-drug interaction information, however, cannot be reliably extrapolated to transdermal oxybutynin because the first-pass metabolism of transdermal oxybutynin differs significantly from oral oxybutynin.*

1.3.6 Specific Populations

Gender: Although OTG is indicated for adult patients with overactive bladder, the target population will be primarily older women. The sponsor did not enroll sufficient men to perform a meaningful subset safety analysis based on gender from the controlled safety studies data.

In phase 1 PK studies in healthy volunteers, female volunteers showed slightly greater oxybutynin absorption and metabolism than the male volunteers. The clinical significance of this difference is unknown.

Race: The number of minorities was too small to perform an adequate subset safety analysis based on race from the controlled safety studies data.

Age: In the phase 3 study, approximately 35% of randomized patients were ≥ 65 years old. No overall differences in safety or efficacy were noted between these patients and younger patients.

Renal impairment: OTG has not been evaluated in patients with renal impairment.

Hepatic impairment: OTG has not been evaluated in patients with hepatic impairment.

Pediatric: OTG has not been evaluated in patients < 18 years old. The sponsor requests a waiver for conducting pediatric studies in children from birth through 4 years of age and a deferral of conducting studies in children 5-17 years old until after OTG is approved for use in adults.

Reviewer's comment: *The Pediatric Review Committee (PeRC) granted a pediatric waiver for children ages 0 to 5 years, 11 months, and a pediatric deferral for children ages 6 to 16 years, 11 months. This decision is consistent with previous pediatric waiver and deferrals granted to other anticholinergic products indicated for the treatment of OAB in adults.*

Pregnancy: Oxybutynin is a pregnancy category B based on negative teratogenic findings in preclinical studies. The safety of oxybutynin administration to pregnant women has not been established.

2 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

Oxybutynin Transdermal Gel 10% is a clear, smooth hydroalcoholic gel containing 100 mg oxybutynin chloride per gram of gel. OTG 10% is available in a 1 gram (1.14 mL) unit dose containing 100 mg oxybutynin chloride. Each unit dose is packaged in individual sachets constructed of one of two multi-layer, foil-based laminate pouching materials. A topically applied unit dose has a nominal *in vivo* delivery rate of 4 mg oxybutynin per day through intact skin. Oxybutynin is delivered as a racemate of R- and S-isomers. Inactive ingredients in OTG 10% are alcohol, USP; glycerin, USP; hydroxypropyl cellulose, NF; sodium hydroxide, NF; and purified water, USP. The quantitative composition of the drug production is provided below in Table 2.

Table 2: Composition of OTG 10%

Component	% by Weight	mg/g	Function
Oxybutynin chloride, USP	10.0	100	Drug Substance
Purified Water, USP	(b) (4)		
Alcohol, USP			
Glycerin, USP			
Sodium Hydroxide, (b) (4) (Sodium Hydroxide, NF and Purified Water, USP)			
Hydroxypropyl Cellulose, NF			

Source: Module 2.3, Drug Product, Description of Composition of Drug Product, Table 2.3.1-2, p. 1

2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATION

Overactive bladder (OAB) is a symptom complex comprising chronic symptoms of frequency and urgency with or without urge urinary incontinence (U-UI). These symptoms must be exhibited in the absence of pathological or metabolic disorders (e.g., urinary tract infection, bladder cancer) that might cause such symptoms. In the U.S., approximately 17% of the general adult population, or 33 million adults, meet the criteria for OAB, with one-third of these patients experiencing urinary urge incontinence.[3] The prevalence of OAB increases with age, and more women than men experience U-UI. Overactive bladder has significant impact on the patient's quality of life, ranging from sleep disturbance to interference with social activities to fall and fracture. The mainstays of OAB therapy include patient education, behavioral modifications (e.g., fluid management, timed voiding, bladder drills, prompted voiding), pelvic-floor physical therapy, anticholinergic medications, and rarely, electrical stimulation therapy and surgery in refractory cases. The management of OAB is usually a step-wise approach. Behavioral therapy, which typically includes a combination of patient education, behavioral modifications and pelvic floor muscle exercises, is often the first-line treatment. These conservative measures have been shown to be effective in controlling OAB symptoms in studies of limited duration. Patient compliance with these conservative measures, however, often declines with time because they require significant time and effort on the part of the patient to remain effective.

If the conservative approach is unsuccessful, antimuscarinic pharmacotherapy is added to the regimen of OAB therapy. These drug therapies include oral (immediate release and extended release) and transdermal formulations (Oxytrol transdermal system [Oxytrol TDS]). The approved oral antimuscarinic medications are oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. A systematic literature review found that, compared to placebo, treatment with these agents resulted in a 40% higher rate of cure or improvement, and an absolute mean improvement of 0.6 in both incontinence episodes and voids per day. The absolute treatment benefit over placebo was small, in part because patients who received placebo also did well. This may be due to concomitant bladder training in some of the studies, or training effects from completion of multiple bladder diaries during the trial.[4] Although there are no head-to-head comparison studies, no compelling evidence exists to indicate that one antimuscarinic agent is superior to another in efficacy.[5]

All oral antimuscarinic agents produce adverse reactions resulting from the pharmacologic blockade of cholinergic receptors throughout the body. Examples include inhibition of muscarinic receptors in the salivary gland (dry mouth), the gut (constipation), ciliary muscle of the lens (blurry vision for near objects), heart (tachycardia), and central nervous system (drowsiness, altered cognitive function). The specific safety profile of each antimuscarinic product depends, in part, on its relative affinity for each muscarinic receptor subtype and its PK profile. Extended-release formulations of oxybutynin (Ditropan XL) and tolterodine (Detrol LA) were developed to achieve more consistently steady plasma concentrations and improve tolerability compared with their immediate-release counterpart. However, anticholinergic side effects continue to be a major cause of patient noncompliance and treatment discontinuation.

A transdermal formulation of oxybutynin (Oxytrol TDS) was developed in an attempt to reduce some of the systemic anticholinergic side effects. Unlike the oral route, transdermal delivery of oxybutynin avoids the extensive first-pass metabolism, which leads to decreased conversion of oxybutynin to N-desethyloxybutynin (DEO), a major pharmacologically active metabolite thought to contribute to the anticholinergic side effects. The continuous delivery of oxybutynin via the transdermal route avoids the peak and trough concentrations seen with oral formulation, which may also contribute to improved tolerability. In controlled clinical trials with Oxytrol TDS, the incidence of dry mouth was comparable to

that of placebo, and the incidence of patients discontinuing treatment due to anticholinergic side effects appeared to be less than that observed in clinical trials with oral oxybutynin. However, application site reactions associated with the transdermal delivery system were frequently reported and were the most common reason for treatment discontinuation.

2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES

Oxybutynin is available in immediate release (IR), extended release (ER), and transdermal formulations. A summary of the product information of approved oxybutynin products are presented in Table 3. The approval history of these products follows:

- NDA 17-577 for oxybutynin chloride 5 mg tablets (Ditropan®) was approved in July, 1975. The product was approved for use in both adult and pediatric populations.
- NDA 18-211 for oxybutynin chloride 5 mg/5 mL syrup (Ditropan®) was approved in November, 1979. The product was approved for use in both adult and pediatric populations.
- NDA 20-897 for oxybutynin chloride extended release (Ditropan® XL) 5, 10, and 15 mg extended-release tablets was approved for use in adults in December, 1998. The product was approved for use in the pediatric population (≥ 6 years old) in April, 2003, after the terms of the Written Request were sufficiently fulfilled.
- NDA 21-351 for oxybutynin chloride transdermal system (Oxytrol® TDS) (3.9 mg/day, change patch every 3-4 days) was approved for use in adults in March, 2003.

Table 3: Product Information of Approved Oxybutynin Products

Trade name	**Ditropan®**	**Ditropan® XL**	**Oxytrol®**
Formulation	IR oral tablet and syrup	ER oral tablet	Transdermal patch
Labeled Indication	"Relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder (i.e. urgency, frequency, urinary leakage, urge incontinence, dysuria)"	Same as Ditropan®	"Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency"
Dose and dosing regimens	Tablet: 5 mg Syrup: 5 mg/5 mL <u>Adults</u>: Start with 2.5 mg bid to tid, increase in increments up to maximum of 20 mg/day in divided doses as needed <u>Pediatric patients</u>: 5 mg bid, up to maximum of 5 mg tid	5 mg, 10 mg, 15 mg <u>Adults</u>: Start with 5 or 10 mg once daily, increase in 5 mg increments as necessary (maximum of 30 mg/day) <u>Pediatric patients</u> (≥ 6 years): 5 mg once daily, increase in 5 mg increments as needed (maximum of 20 mg/day)	3.9 mg/day (39 cm^2 patch) Change one system (3.9 mg/day) every 3 to 4 days
Intended population	Adult and pediatric patients (≥ 6 years) with bladder instability due to detrusor instability or neurogenic bladder	Same as Ditropan®	Adults with OAB

Source: Ditropan®, Ditropan® XL, Oxytrol® product labels

2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS

Labeled safety issues with oxybutynin:

- Use is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients at high risk for these conditions.
- Use with caution in patients with clinically significant bladder outflow obstruction or gastrointestinal obstructive or motility disorders, myasthenia gravis, hepatic or renal impairment, or the frail elderly.
- Use with caution in patients with pre-existing dementia treated with cholinesterase inhibitors due to the risk of aggravation of symptoms (in oral oxybutynin product label).
- Monitor for central nervous system effects (e.g., hallucinations, agitation, confusion, and somnolence) during first few months of drug use or with dose increase (in oral oxybutynin product label).
- Symptoms of hyperthyroidism, coronary artery heart disease, congestive heart failure, cardiac arrhythmias, hiatal hernia, tachycardia, hypertension, and prostatic hypertrophy may be aggravated.
- Common adverse reactions are those associated with anticholinergic effects (e.g., dry mouth, dizziness, constipation, nausea, blurred vision, heat prostration).

Safety issues related to transdermal formulation:

- Adverse application site reactions include application site pruritus, erythema, macules, rash, and vesicles, with application site pruritus and erythema being the most common. In controlled clinical trials, application site reactions were reported by 16-21% Oxytrol TDS-exposed patients, 5% of whom reported severe reactions. In the same studies, dermatologic reactions led to premature discontinuation in approximately 10% of Oxytrol TDS-exposed patients. Rarely, cases of contact sensitization have been observed in clinical trials with active TDS treatment.
- Person-to-person transference: Direct physical contact at the application site of gel products (e.g., testosterone) can result in systemic drug absorption in untreated partners. The risk of skin-to-skin transference may be significantly reduced by covering the application site with clothing.
- Topical gels containing alcohol are flammable and open flame/smoking should be avoided during the application of these gel products.

2.5 PRESUBMISSION REGULATORY ACTIVITY

The sponsor opened IND 67,126 (oxybutynin transdermal gel 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 OTG, the sponsor planned to conduct one large phase 3 with 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 OTG 10%.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC and PRODUCT MICROBIOLOGY

Chemistry: At this time, CMC is unable to recommend approval of this NDA until the Office of Compliance establishes that the manufacturing sites are acceptable. From a chemistry perspective, the NDA has provided sufficient information to assure the identity, purity, and quality of the drug product.

Microbiology: Recommends approval from a microbiology perspective.

3.2 ANIMAL PHARMACOLOGY AND TOXICOLOGY

Recommends approval from a pharmacology/toxicology perspective.

3.3 CLINICAL PHARMACOLOGY

Recommends approval from a clinical pharmacology perspective. The clinical pharmacology reviewer concludes that the sponsor has demonstrated that the systemic exposure of oxybutynin from OTG and the currently approved transdermal patch are similar.

3.4 STATISTICS

Recommends approval from a statistical perspective. The statistics reviewer recommends that the p-values for the secondary endpoints not be included in the label because they were not pre-specified and there were no statistical adjustment for testing multiple endpoints.

Reviewer's comment: *During an internal DRUP meeting, the DRUP clinical and statistic review teams agreed that the p-value for the secondary endpoint of urinary frequency may be labeled because of the following reasons: 1) it is a clinically meaningful endpoint for OAB and, 2) the results of the statistical testing of the primary endpoint and the secondary endpoints were robust and persuasive. Because the clinical significance of the secondary endpoint of average urine volume voided was questionable, the teams concluded that the results of this endpoint should be presented in a descriptive manner in the product label.*

During the labeling negotiations teleconference on January 13, 2009, the Division agreed to allow the inclusion of the p-values for the secondary endpoints of urinary frequency and average volume voided, primarily because statistical significance data for these 2 secondary endpoints were allowed in all other OAB drug labels.

3.5 CONSULTS FROM OTHER DIVISIONS

3.5.1 Division of Scientific Inspection (DSI)

Because there was only one phase 3 study to support the safety and efficacy of OTG, the Division consulted DSI to conduct a routine inspection of 2 large study sites. DSI inspected 2 study sites with large enrollment numbers (Dr. Schmidth-24 subjects; Dr. Deeths-35 subjects) and found no irregularities. DSI concludes that no action is indicated.

3.5.2 Office of Surveillance and Epidemiology (OSE)

- Division of Medication Error Prevention and Analysis (DMEPA): DMEPA accepts the tradename of "Gelnique" and also accepts the revised carton container label, which incorporated all of DMEPA's recommendations.
- Division of Risk Management (DRISK): DRISK's recommendations have been incorporated into the final Patient Labeling agreed upon by the Division and the sponsor.

3.5.3 Study Endpoints and Labeling Development Team (SEALD):
SEALD's recommendations were incorporated into the final product label agreed upon by the Division and the sponsor.

3.5.4 Division of Drug Marketing, Advertising, and Communications (DDMAC):
DDMAC's recommendations were incorporated into the final product label agreed upon by the Division and the sponsor.

3.5.5 Pediatric Review Committee (PeRC)

- Pediatric waiver (0-4 years): A pediatric waiver was requested and granted for OTG in children ages 0 to 5 years, 11 months.
- Pediatric deferral (5-16 years old): A pediatric deferral was requested and granted for OTG in children ages 6 to 16 years, 11 months. See Section 8.3 (Special Populations-Pediatrics) of this clinical review for further details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 SOURCES OF CLINICAL DATA

This NDA was submitted entirely in the electronic Common Technical Document (eCTD) format. The following materials were reviewed:

a. Overview section, clinical summaries, and integrated summary of safety
b. Clinical safety and efficacy: Study **OG05009** (" A multi-center, double-blind, placebo-controlled study of the efficacy and safety of daily dosing with Oxybutynin Topical Gel to treat the symptoms of overactive bladder with a 14-week open-label safety extension")
c. Comparative pharmacokinetics: Study **OG04007** ("Single-dose pharmacokinetics of oxybutynin and metabolites following transdermal applications of 3.9 mg/day Oxytrol transdermal system, 3 g of 4.4% topical oxybutynin gel, 1 g of 10% topical oxybutynin gel and 3 g of 10% topical oxybutynin gel to healthy volunteers") and Study **OG06005** ("A steady-state comparison of plasma oxybutynin, N-desethyloxybutynin and R and S enantiomers concentrations following multiple dose application of 1 g oxybutynin topical gel and Oxytrol oxybutynin transdermal system in healthy volunteers")
d. Dermatoxicity: Study **OG05003** (cumulative irritation study) and **OG05004** (skin sensitization study)
e. Other PK studies affecting safety: Study **OG06007** (person-to-person transference) and Study **OG06006** (effect of sunscreen lotion on OTG absorption)
f. 120-Day Safety Update
g. Annual IND reports for IND 67,126, Annual ADE reporting for NDA 21-351 (Oxytrol), Annual NDA report for NDA 21-351

4.2 TABLE OF CLINICAL STUDIES

Table 4 summarizes the clinical studies used to support the safety and efficacy of OTG. All studies, except for OG02020, were conducted in the U.S. under IND 67,126.

Table 4: **Summary of Clinical Studies with OTG**

Type of Study	Objective	Test product	Treatment duration	# of subjects (M/F)
Phase 1				Healthy subjects
OG02020	Bioavailability (BA) and pharmacokinetics (PK)	3 g 4.4% once daily	3 days	12 (10/2)
OG03013	Surface area of application on BA	3 g 4.4% single dose	2 days	22 (11/11)
OG03018	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose, 1 g 13.2% single dose	2 days	22 (10/12)
OG04004	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose 1 g 13.2% single dose	2 days	20 (10/10)
OG04007*	Comparative BA and PK of 3 different OTG formulations and Oxytrol	3 g 4.4% single dose 1 g 10% single dose 3 g 10% single dose 3.9 mg/day Oxytrol single application (one TDS for 3.5 days)	6.5 days	22 (13/9)
OG03005	Steady state BA and PK	3 g 4.4% once daily	8 days	20 (11/9)
OG04008*	Steady state PK and application site bioequivalence	1 g 10% once daily	42 days	40 (20/20)
OG06005*	Steady state PK and comparison with Oxytrol	1 g 10% once daily Oxytrol x 4 applications (each application = 3.5 days)	36 days	22 (12/10)
OG06001*	Effect of sunscreen	1 g 10% single dose	3 days	16 (8/8)
OG06006*	Effect of showering	1 g 10% once daily	35 days	20 (9/11)
OG06007*	Transfer potential	1 g 10% single dose	1 day	52 (25/27)
Dermatoxicity studies				Healthy subjects
OG05003*	Cumulative irritation	1 g 10% once daily	21 days	45 (14/31)

		1 g placebo once daily		
OG05004	Skin sensitization	0.5 g 10% three times per week for 3 weeks 0.5 g placebo gel 3 times per week for 3 weeks	22 days	225 (87/138)
Phase 3 safety and efficacy				OAB patients
OG05009-double blind*	Safety and efficacy of 1g 10% OTG in target population	1 g 10% once daily 1 g placebo once daily	12 weeks	789 389 OTG (37/352) 400 plac (48/352)
OG05009-open label*	Safety	1 g 10% once daily	14 weeks	216 (22/194)

*Studies using the to-be-marketed dose and formulation (1 g 10% OTG)
Source: Synopses of Individual Studies, Module 2.7.6, Table 2.7.6-1, p. 4-6

4.3 REVIEW STRATEGY

All materials submitted in the NDA were considered during the conduct of this clinical review. Specific details regarding the approach used to conduct this review are outlined below:

- The clinical efficacy review was based entirely on Study OG05009; the safety review included the integrated Study OG05009, the 10 integrated phase 1 studies, the 2 non-integrated dermatoxicity studies, and the non-integrated person-to-person transference study.
- The focus of the efficacy and safety review was Study OG05009 double-blind period. This was the only adequate and well-controlled clinical study appropriately designed to assess drug effect on safety and efficacy.
- Comparative PK studies (OG04007 and OG06005) were reviewed in detail in the clinical pharmacology section to assess the similarity of PK parameters between 1 g 10% OTG and Oxytrol TDS. Pharmacokinetic data pertinent to proposed labeling from the other phase 1 clinical pharmacology studies were reviewed.
- The 2 dermatoxicity studies (OG05003, OG05004), the person-to-person transference study (OG06007), and the sunscreen study (OG06001) were reviewed in detail, and these reviews are contained in Appendices 10.1.2 to 10.1.5, respectively.
- Independent analyses of datasets of the original efficacy and safety variables were conducted throughout the clinical review to explore certain safety/efficacy issues of interest and to verify the sponsor's findings.

4.4 DATA QUALITY AND INTEGRITY

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."

Central laboratory: In OG05009, laboratory testing for safety parameters was performed by (b) (4) [redacted] Plasma samples

were assayed for concentrations of oxybutynin and DEO according to a validated liquid chromatography/mass spectrometry (LC/MS) method developed and validated by (b) (4)

Site Monitoring: Study OG05009 study sites were monitored and audited by (b) (4). Audit certificates indicating GCP compliance were submitted for 7 study sites.

Standard Operating Procedures: The sponsor has in place standard operating procedures that are consistent with ICH Good Clinical Practice, which include archiving of source data, data validation of CRF data, internal audits, documentation of the qualifications of investigators, and the use of a validated central laboratory.

4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES

According to the sponsor, all clinical studies submitted were conducted in compliance with Good Clinical Practices. In support of this, the sponsor submitted samples of informed consent, documents of IRB approval, and required case report forms.

4.6 FINANCIAL DISCLOSURES

Form FDA 3454 (4/06), dated January 18, 2008, and signed by Kevin Barber, Ph.D., Executive Director, Proprietary Regulatory Affairs, Watson Laboratories, was 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 will be 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 [21 CFR 54.2(a)], proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product [21 CFR 54.2(b)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.2(f)]. 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.

5 CLINICAL PHARMACOLOGY

5.1 PHARMACOKINETICS

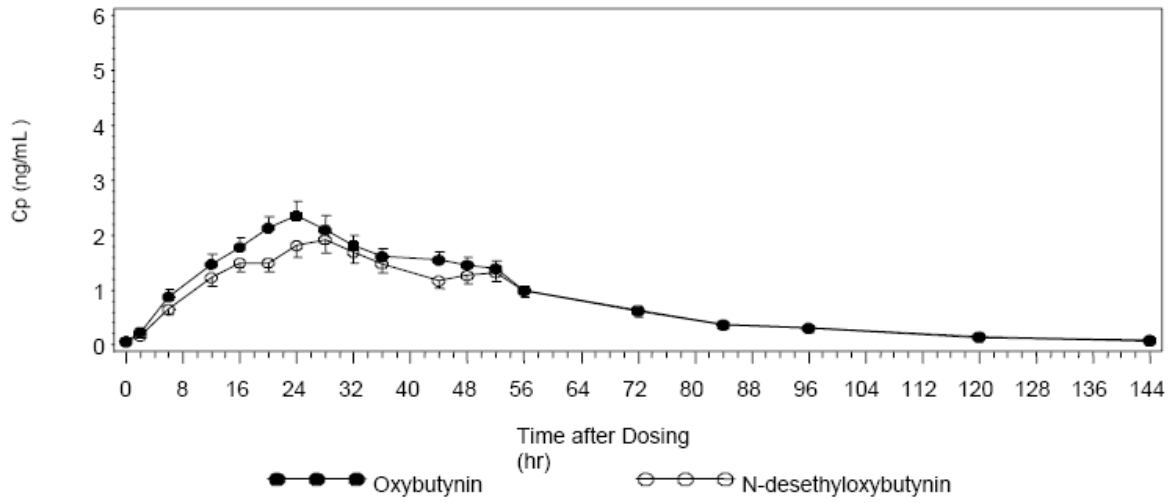
5.1.1 Drug product pharmacokinetics

Absorption:

Single dose: Transdermal oxybutynin is absorbed through the skin and into systemic circulation by passive diffusion. The estimated nominal dose of oxybutynin absorbed from 1 g 10% OTG is approximately 4 mg, or 4% of the applied dose, based on comparative PK studies with Oxytrol TDS (3.9 mg/day). Plasma oxybutynin profiles after a single-dose of 1 g 10% OTG showed a short lag phase to establish transport through the skin followed by a steady increase in plasma oxybutynin concentrations

occurring during the initial 24 hours after drug application, followed by a slow decline in concentrations thereafter. Figure 1 summarizes the pharmacokinetics of oxybutynin and N-desthyloxybutynin (DEO) after a single dose of 1 g 10% OTG.

Figure 1: Mean (± SEM) plasma oxybutynin and N-desethyloxybutynin concentrations following a single 1 gm dose of 10% OTG. (Study OG04007)



Multiple dose: Steady state PK for oxybutynin and DEO following multiple applications (7 days) of 3 g 4.4% OTG was evaluated in study OG03005 following a 7-day washout period after the single dose study. According to the clinical pharmacology reviewer, steady state may have been reached after the second dose. Multiple dose PK was evaluated for the 1 g 10% OTG formulation in study OG04008. Based on racemic oxybutynin and DEO plasma concentrations, oxybutynin absorption was similar when OTG was applied to the abdomen, thighs, or upper arms (see Table 5).

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Table 5: Relative Bioavailability of 1 g 10% OTG at Different Application Sites

Variable	Comparison (Test:Reference)	PK Parameter	Ratio	90% Confidence Interval	Bioequivalence Achieved?
Oxybutynin	Thigh: Abdomen	$AUC_{[0-24]}$	1.07	0.93,1.23	YES
		C_{max}	0.99	0.85,1.16	YES
	Arm:Abdomen	$AUC_{[0-24]}$	1.14	0.99,1.31	NO
		C_{max}	1.14	0.97,1.33	NO
DEO	Thigh: Abdomen	$AUC_{[0-24]}$	1.09	0.95,1.26	NO
		C_{max}	1.11	0.96,1.28	NO
	Arm:Abdomen	$AUC_{[0-24]}$	1.09	0.94,1.25	NO
		C_{max}	1.13	0.98,1.30	NO

Source: Study report, Table 11-5, p. 31

***Reviewer's comment**: Using the abdomen as the reference site, bioequivalence of AUC and Cmax for oxybutynin was achieved only between the thigh and abdominal sites, based on 90% confidence intervals.*

DEO concentrations were not strictly bioequivalent between thigh and abdominal sites or for the upper arm and abdomen for either parameter. Although strict bioequivalence was not achieved based on the 90% confidence intervals, the clinical pharmacology team concluded that the 3 application sites produced similar oxybutynin bioavailability. The magnitude of the differences between the 3 application sites is small compared to the oxybutynin/DEO exposure after oral oxybutynin administration and is not expected to produce clinically important differences in safety and efficacy. Furthermore, patients in the phase 3 study used all 3 application sites on a rotating schedule.

Metabolism: Oxybutynin is metabolized primarily by the cytochrome P450 enzyme systems, particularly CYP3A4, found mostly in the liver and gut wall. Small amounts of CYP3A4 are found in the skin. Metabolites include phenylcyclohexylglycolic acid, which is pharmacologically inactive, and DEO, which is pharmacologically active. Transdermal administration of oxybutynin bypasses the first-pass gastrointestinal and hepatic metabolism. The AUC ratio of DEO: oxybutynin after multiple doses of 1 g 10% OTG was approximately 1.

Elimination: After multiple applications of 1 g 10% OTG, both oxybutynin and DEO showed biphasic elimination with blood concentrations declining starting at 24 hours post-dose. Elimination was more rapid between 24 and 48 hours after dosing, during which time plasma concentrations of oxybutynin and DEO declined by about 50%. This was followed by a more prolonged terminal elimination phase. The apparent elimination half-lives were 64 hours for oxybutynin and 82 hours for DEO.

Dose-proportionality of pharmacokinetics: No dose proportionality studies with the final OTG formulation were conducted. In a single-dose, 4-way crossover PK study of 1 g 10% OTG and 3 g 10% OTG, AUC and Cmax values more than slightly doubled (less than dose-proportional) when the dose was increased from 1 g to 3 g; the $t_{1/2}$ and t_{max} remained unchanged.

5.1.2 Intrinsic Factors

Gender: In general, female subjects had higher oxybutynin and DEO concentrations (approximately 20-30%) as well as higher DEO:OXY AUC ratios than male subjects. However, these differences are not expected to be clinically significant.

Reviewer's comment: *According to the clinical review of NDA 21-351 (Oxytrol TDS 3.9 mg/day), mean plasma oxybutynin concentrations were generally somewhat higher in males than in females while DEO concentrations were generally higher in females. The clinical implications of these gender differences are unknown but are unlikely to pose any meaningful safety issues.*

Pharmacokinetic studies to evaluate 1 g 10% OTG in the pediatric population or in subjects with renal impairment, liver insufficiency, or other disease states were not performed.

5.1.3 Extrinsic Factors

Showering: Oxybutynin absorption was not affected by showering 1, 2, or 6 hours after application, compared to no shower. Compared to no shower, showering decreased the time to maximum concentration (Tmax) closer to the time of showering (usually within 2 hours of showering), and the change in Tmax is not unlikely to impact safety or efficacy.

Sunscreen: Sunscreen application 30 minutes before or after OTG application did not affect oxybutynin absorption or metabolism.

Person-to-person transference: OTG can be transferred from a treated person to an untreated person via direct skin-to-skin contact at the application site. This dermal transference can be significantly reduced by covering the application site with clothing.

Drug-drug interactions: No studies were performed with OTG.

5.1.4 Population Pharmacokinetics

In the phase 3 study double-blind period, blood samples were obtained from all enrolled patients using sparse collection techniques for analysis of oxybutynin and DEO plasma concentrations. Mean plasma concentrations of oxybutynin and DEO were similar across all study visits. The sponsor concluded that steady state was achieved by Week 1 by performing a paired t-test of the difference in oxybutynin concentrations at Week 1 and Week 4. A summary of plasma concentrations of oxybutynin and DEO for OTG-treated patients is presented in Table 6.

Table 6: Plasma Concentrations (ng/mL) of Oxybutynin and DEO in Phase 3 Study (mITT)

Analyte*	Week 1 N=364	Week 4 N=357	Week 8 N=338	Week 12 N=308	Endpoint (LOCF)
OXY	6.3 (5.6)	6.1 (5.2)	6.1 (5.4)	6.1 (5.9)	6.0 (5.9)
DEO	6.7 (6.3)	6.7 (6.5)	6.8 (7.1)	7.2 (7.8)	7.1 (8.0)
DEO:OXY	1.13 (0.5)	1.16 (0.6)	1.18 (0.7)	1.2 (1.0)	1.2 (1.0)

*Blood concentrations expressed as mean (SD), Source: Study report, Table 14.4-1, p. 3279-80

Plasma concentrations of oxybutynin and DEO were summarized for gender, race (Caucasian versus non-Caucasian), geriatric status (< 65 years old versus ≥ 65 years old), and BMI category (< 32 kg/m^2 versus ≥ 32 kg/m^2). Overall, the following groups had slightly higher oxybutynin concentrations than their comparative counterpart: women, Caucasians, and geriatric patients. No differences were observed between the two BMI categories. See Table 7.

Table 7: Plasma Concentrations (ng/mL) of Oxybutynin and DEO at Endpoint by Subgroups

Analyte*	Geriatric		Gender		Ethnicity	
	< 65 years	≥ 65 years	Males	Females	Caucasian	Non-caucasian
N	243	137	35	345	337	43
OXY	5.5 (6.1)	6.8 (5.4)	3.9 (2.8)	6.2 (6.1)	6.2 (6.0)	3.9 (4.4)
DEO	6.4 (7.8)	8.3 (8.4)	4.2 (3.5)	7.4 (8.3)	7.4 (8.2)	5.1 (6.4)
DEO:OXY	1.2 (0.9)	1.3 (1.1)	1.3 (1.8)	1.2 (0.8)	1.2 (0.9)	1.3 (1.2)

*Blood concentrations expressed as mean (SD)
Source: Study report, Tables 14.4-2 to 14.4-4, p. 3289-3300

Reviewer's comment: *Other than geriatric patients, too few males and non-Caucasians were enrolled to draw meaningful conclusions. Given the extensive inter-subject variability in oxybutynin and DEO exposure, these differences are unlikely to result in clinically significant differences in safety or efficacy.*

5.1.5 Comparative Pharmacokinetics

Study OG04007 (single-dose): This was a single-dose, 4-period, open-label, randomized, crossover investigation comparing the PK of Oxytrol TDS (3.9 mg/day), 3 g 4.4% OTG, 3 g 10% OTG, and 1 g 10% OTG. The sequence of treatment was randomized for each subject, with a 7-day washout period

between each treatment. Serial blood sampling was obtained for 144 hours for each treatment period. The abdomen was the only application site used in this study. Results of the study are summarized in Table 8.

Table 8: Mean (SD) PK Values of Summed OXY + DEO Concentrations (N=20)

Parameter (OXY+DEO)	Oxytrol TDS	1 g 10% OTG	3 g 10% OTG	3 g 4.4% OTG
AUC_{0-144} (ng/mL.hr)	614.4 (230.2)	219.5 (78.5)	498.9 (212.4)	325.0 (110.9)
Normalized AUC (ng/mL)*	175.54 (65.8)	219.5 (78.5)	498.9 (212.4)	325.0 (110.9)
Cmax (ng/mL)	8.61 (3.5)	4.67 (1.9)	9.9 (5.6)	6.4 (2.4)
T ½ (h)	18.6 (4.4)	28.4 (11.9)	26.7 (8.5)	26.1 (6.2)
Median Tmax (h)	28.0	24.0	26.0	26.0
DEO:OXY	1.06 (0.4)	0.90 (0.4)	0.85 (0.4)	0.88 (0.3)

*A dose-normalized AUC was calculated for each Oxytrol application that individually divided the Oxytrol AUC (0-144) by 3.5 days to compare to a daily gel application.
Source: Study report, Synopsis and Tables 11-1 to 11-5, p. 2, p. 29-34

Based on a best-fit plasma concentration-time profile modeling using the measured single-dose plasma concentration data to predict plasma concentration profiles for 14 days of dosing, daily doses of 1 g 10% OTG appeared to provide steady state PK characteristics comparable to that of Oxytrol TDS applied every 3-4 days.

Study OG06005 (steady-state): This was an open-label, 2-period, multiple dose, randomized, crossover study evaluating the comparative steady state PK of 1 g 10% OTG and Oxytrol TDS. Subjects were treated with 18 daily doses of 1 g 10% OTG and 5 consecutive applications of Oxytrol TDS (4 applications x 3.5 days per application, followed by one final 4-day application) in a randomized sequence. Blood sampling was for plasma oxybutynin, DEO, and enantiomer concentrations measurements at 0 hours (immediately prior to the gel/TDS application), and at 12, 24, 36, 48, 60, 72, 84 and 96 hours following the final 4-day application of the TDS and final 4 daily applications of OTG. A minimum 14-day washout separated the two treatment regimens. The sequence of application sites for Oxytrol (abdomen/buttocks/hip) and OTG (abdomen/thigh/upper arm) was randomized for each subject. Results of comparative PK are summarized in Table 9.

Table 9: Summary of Oxybutynin and DEO PK by Treatment

PK Parameter*	Analyte	1 g 10% OTG N=20	3.9 mg/dayTDS N=20
$AUC_{(0-96)}$ (ng.hr/mL)	OXY DEO DEO:OXY	321.7 (112.3) 264.4 (97.0) 0.77 (0.2)	312.5 (67.6) 338.0 (116.9) 1.07 (0.22)
C_{avg} (ng/mL)	OXY DEO	3.35 (1.17) 2.57 (1.01)	3.26 (0.7) 3.52 (1.22)
C_{max} (ng/mL)	OXY DEO	5.99 (2.58) 4.35 (2.3)	4.82 (1.31) 4.98 (1.7)
T_{max} (h)	OXY DEO	36.0 (33.0) 44.4 (32.1)	40.8 (23.5) 35.4 (20.0)

*All values are expressed in mean (SD) values
Source: Study report, Tables 11-3 and 11-4, p. 27-28

The mean (SD) $AUC_{(0\text{-}96\ h)}$ ratios of DEO:OXY for OTG was 0.77 (0.2) and 1.07 (0.2) for TDS, indicating that oxybutynin delivered by the gel formulation underwent less metabolism than a patch formulation. Results of concentrations and PK parameters of oxybutynin and DEO enantiomers are summarized in the Tables 10 and 11.

Table 10: Summary of R- and S-Oxybutynin Pharmacokinetics by Treatment

Parameter*	OTG		TDS	
	R-OXY	S-OXY	R-OXY	S-OXY
$AUC_{0\text{-}96}$ (ng.h/mL)	143.3 (47.9)	178.3 (65.0)	138.6 (29.7)	173.9 (39.8)
C_{avg} (ng/mL)	1.49 (0.5)	1.86 (0.7)	1.44 (0.3)	1.81 (0.4)
C_{max} (ng/mL)	2.67 (1.1)	3.32 (1.5)	2.11 (0.6)	2.72 (0.7)
C_{min} (ng/mL)	0.81 (0.2)	0.97 (0.23)	0.79 (0.2)	0.98 (0.4)
T_{max} (h)	34.8 (32.1)	36.0 (33.0)	41.4 (23.2)	37.8 (21.8)

*PK parameters are expressed in mean (SD) values
Source: Study report, Table 11-7, p. 31

Reviewer's comment: *At steady state, the oxybutynin concentrations and PK parameters of OTG were similar to those of Oxytrol TDS. For both products, S-OXY concentration and exposure were approximately 25% higher than R-OXY concentrations.*

Table 11: Summary of R- and S-DEO Pharmacokinetics by Treatment

Parameter*	OTG		TDS	
	R-DEO	S-DEO	R-DEO	S-DEO
$AUC_{0\text{-}96}$ (ng.h/mL)	143.2 (45.9)	103.2 (57.0)	197.4 (74.7)	140.6 (64.0)
C_{avg} (ng/mL)	1.49 (0.5)	1.07 (0.6)	2.06 (0.8)	1.46 (0.7)
C_{max} (ng/mL)	2.51 (1.2)	1.86 (1.2)	2.96 (1.1)	2.06 (0.9)
C_{min} (ng/mL)	0.86 (0.2)	0.61 (0.3)	1.2 (0.5)	0.9 (0.5)
T_{max} (h)	45.0 (31.4)	51 (30.4)	31.2 (17.2)	33.0 (22.7)

*PK parameters are expressed in mean (SD) values
Source: Study report, Table 11-8, p. 32

The $AUC_{(0\text{-}96)}$ DEO:OXY ratios for R and S isomers indicate slightly greater metabolism following TDS dosing than OTG dosing. The ratios for R-isomer for TDS and OTG were 1.41 and 1.03, respectively. The ratios for S-isomer for TDS and OTG were 0.78 and 0.56, respectively.

Reviewer's comment:

- *At steady state, DEO concentration and exposure (Cavg, AUC) was approximately 25% less after OTG dosing than Oxytrol dosing.*
- *Although DEO is a pharmacologically active metabolite, the implication of these differences on clinical efficacy is unknown, in part, because the exposure-response relationship of DEO is not well-characterized.*
- *According to the clinical pharmacology reviewer, the concentration and exposure of OXY + DEO were similar after Oxytrol TDS and OTG dosing.*

5.3 EXPOSURE-RESPONSE RELATIONSHIP

Exploratory exposure-response analyses were conducted by using linear regression to test whether there was a linear relationship between the changes from baseline in the primary and key secondary efficacy

endpoints and plasma concentrations of oxybutynin and DEO. There was no significant correlation between oxybutynin or DEO concentrations and the key efficacy endpoints.

5.4 CLINICAL PHARMACOLOGY CONCLUSIONS

- 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 a 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 those observed in clinical pharmacokinetic studies.

6 INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

The sponsor seeks the indication of "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency."

6.1.1 Methods

The primary objective of the efficacy review was to assess whether OTG treatment resulted in clinically and statistically significant improvement in OAB symptoms over placebo. The efficacy assessment was based entirely on the findings of Study OG05009, as this was the only study in the clinical development of OTG that evaluated the clinical outcomes of OTG treatment. The efficacy findings of Study OG05009 were reviewed in detail in this section; independent analyses of the submitted datasets of OG05009 were conducted to verify the sponsor's efficacy findings; and the treatment effect of OTG was compared to those of other approved OAB products for consistency of performance.

6.1.2 General Discussion of Endpoints

Registration of OAB drug treatment in the U.S. is generally based on the treatment effect on the number of urinary incontinence episodes, urinary frequency, or both.

- <u>Number of incontinence episodes per day</u>: The data for this endpoint is usually captured by patient-reported urinary diary (3-day or 7-day diary). This is an accepted primary clinical endpoint in phase 3 trials for OAB treatment.
- <u>Urinary frequency</u>: Because a significant proportion of OAB patients do not have urinary incontinence and experience only urinary urgency and frequency, urinary frequency is usually a key secondary endpoint or sometimes used as a co-primary endpoint.
- <u>Average urine volume per void</u>: This clinical endpoint provides supportive evidence of an anticholinergic effect on the bladder (increase in bladder capacity) and usually serves as a secondary endpoint.
- <u>Incontinence-specific Quality of Life (QoL) patient-report outcome instruments</u>:

a. King's Health Questionnaire (KHQ): The KHQ is a condition-specific, 21-item instrument that measures the impact of urinary incontinence on multiple and broad aspects of health-related quality of life. It consists of 7 multi-item domains (role limitations, social limitations, personal relationships, emotions, sleep and energy, and severity [coping] measures). In addition, 2 one-item questions address incontinence impact and general health perception. The instrument also includes the multi-item symptom severity scale that measures the severity of urinary symptoms.

b. Incontinence Impact Questionnaire (IIQ): The IIQ is a condition-specific, 30-item instrument that measures the impact of urinary incontinence on 4 domains/subscales: physical activity, travel, social/relationships, and emotional health. All questions are scored on a 4-point Likert scale based on the severity of the impact of UI (0="not at all"; 1="slightly"; 2="moderately"; 3="greatly"). For each subscale, the score ranges from 0-100; the total score, which is a summation of the score of each subscale, ranges from 0-400. The higher the score, the more severe of an impact urinary incontinence has on the patient's health-related quality of life.

6.1.3 Study Design

6.1.3.1 Study Objectives

- Primary: To compare the efficacy of 1 g 10% OTG with placebo gel administered once daily during a 12-week treatment period
- Secondary: To compare additional efficacy measures (urinary frequency, urine void volume, nocturia, quality of life [QoL] evaluations), safety assessment of OTG treatment with placebo. In addition, population pharmacokinetics of oxybutynin and N-desethyloxybutynin were evaluated.
- Open-label: To evaluate the dermatologic safety of chronic OTG use

6.1.3.2 Study conduct and procedures

Study OG05009 was a multicenter, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy and safety of 1 g 10% OTG in the symptomatic improvement of OAB after 12 weeks of treatment. The final study protocol dated June 28, 2006, consisted of 3 periods: screening, double-blind, and open-label safety extension. The original protocol dated September 8, 2005, consisted of a screening period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period (DB period). In Amendment #1 dated June 28, 2006, a 14-week open-label safety extension period (OL period) for approximately 200 patients from sites with the highest enrollment was added to the protocol of OG05009.

Study OG05009 enrolled adult patients with OAB with symptoms of urinary urge incontinence and urinary frequency not related to chronic illness, anatomical weakness or abnormalities, or medication. The initial 2 weeks of the screening period was a washout period for treated patients or a disease stabilization period for treatment-naïve patients. During these 2 weeks, all patients received bladder and fluid management training. These 2 weeks was followed by a 1-week baseline evaluation to complete the 3-day urinary diary, and an additional 1 week, if necessary, to repeat the 3-day urinary diary. Eligible patients then 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 double-blind (DB) period. Clinic visits were scheduled 1 week after the first study

drug dose, then approximately every 4 weeks thereafter (Weeks 1, 4, 8 and 12) (see Appendix 10.1.1 [a] for details of study schedule). The maximum total duration of the screening and DB treatment periods was 16 weeks. Baseline and each follow-up visit included assessment of the following:

- 3-day urinary diary, 2-day voided volume, and QoL questionnaires (King's Health Questionnaire, IIQ). A 3-day urinary diary was recorded during the week immediately prior to the indicated visit beginning at least 4 days prior to the visit. Voided volume of normal voids was recorded on 2 consecutive days of the 3-day diary.
- Vital signs
- Assessment of adverse events, concomitant medications, and skin tolerability
- Sachet counting for compliance assessment

Physical examination, 12-lead ECG, clinical laboratory tests (complete blood count, chemistry, and urinalysis), urine pregnancy test for women of childbearing potential, and post-void residual (PVR) were assessed at baseline and at Week 12/ET visit. Serum Prostate Specific Antigen (PSA) was measured at screening for eligibility purposes.

Pharmacokinetic assessments: Blood was collected for plasma concentration of oxybutynin and DEO during visits occurring at Weeks 1, 4, 8, and 12/ET post-randomization.

Open-label safety extension: All patients enrolled in the open-label (OL) extension period self-administered 1 g 10% OTG daily to rotating sites of the abdomen, upper arms/shoulders, and thighs for 14 weeks. Clinic visits were scheduled for Weeks 19 and 26 post-randomization. During these 2 visits, vital signs, concomitant medications, adverse events, and skin tolerability were assessed. At the Week 26/ET visit, clinical laboratory tests (complete blood count, chemistry, urinalysis, urine pregnancy test for women of childbearing potential) and the QoL questionnaires were also assessed. Urinary diary data were not obtained during the OL period.

The sponsor planned to enroll 700 subjects from 76 study sites for the double-blind period. For the open-label safety extension, the sponsor planned to enroll 200 subjects who completed the double-blind period to ensure that at least 50 subjects received 6 months of active drug.

***Reviewer's comment**: The general study design and procedures are acceptable.*

6.1.3.3 Eligibility Criteria

The study population consisted of patients with a history of urge urinary incontinence and urinary frequency. Urinary symptoms were evaluated during screening through a specific urinary 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, meeting the following criteria as documented by a completed 3-day urinary diary: average of ≥ 8 urinary voids per day, ≥ 4 urge urinary incontinence episodes per 3 days, average urine void volume of ≤ 350 mL per void, and a PVR ≤ 250 mL. Patients were excluded if their OAB symptoms were related to chronic illness, anatomical weakness or abnormalities, or medication use; if they had a history of lower urinary tract surgery within the previous 6 months; a diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome, or one or more treatable conditions that may cause urinary incontinence or urgency (see Appendix 10.1.1 [b] for a comprehensive list of inclusion and exclusion criteria).

***Reviewer's comment**: The eligibility criteria are appropriate for the target population.*

6.1.3.4 Efficacy Endpoints

Primary:

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

Secondary: Change from baseline to Endpoint in the double-blind period in the following:

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

Reviewer's comment: *The Division currently does not accept the IIQ and KHQ questionnaires as valid PRO instruments to support labeling claims. In the 74-Day letter, the Division notified the sponsor that the IIQ and KHQ are considered exploratory endpoints and that the Division did not anticipate including data from these questionnaires in labeling. All currently approved oxybutynin product labels include efficacy data on the number of incontinence episodes, urinary frequency, and average urinary volume per void, although the most clinically meaningful endpoints are urinary frequency and incontinence episodes. The average volume per void is a pharmacodynamic endpoint.*

6.1.3.5 Data Analysis

Statistical issues are discussed in detail in the Statistical Review by the statistics team. A brief overview of the most important statistical analyses is presented in this section. No interim analyses were planned or conducted.

Sample size: Approximately 700 enrolled subjects (350 per treatment group) would provide for 85% power to detect a difference in the change from baseline urinary incontinence episode between active drug and placebo assuming a between-group treatment difference of -0.52 per day at Week 12 (LOCF) (Active = -2.55, Placebo = -2.03), a common standard deviation of 2.25 episodes per day, using a 2-sided test at a significance level of 0.05. Estimates of treatment effect and variability were based on the findings of the most recent safety and efficacy study of Oxytrol (OG002005).

The sample size for the open-label phase was designed to ensure that at least 50 subjects receive a total of 6 months of active drug. By enrolling 200 subjects completing the double-blind phase, approximately 100 would have already received active treatment for 3 months.

Analysis Populations: Four patient populations were defined for statistical analysis:

1. *Modified Intent-to-Treat (mITT):* This was the primary efficacy analysis population and 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.
2. *Intent-to-Treat (ITT):* This was a secondary efficacy analysis population and was defined the same as the mITT population, except in the case of misrandomization, the randomized treatment was to be used in the summary statistics and data analysis.
3. *Evaluable:* This was a secondary efficacy analysis population and included all patients in the mITT population who were without major protocol violations, completed the double-blind period, and provided data for the primary efficacy endpoint at Week 12.
4. *Safety:* All subjects who received at least one dose of study drug.

Datasets: The last-observation-carried-forward (LOCF) and observed cases (OC) datasets were used for summary statistics and data analysis, with the LOCF dataset being the primary.

Efficacy Analyses: All statistical testing were conducted at $\alpha = 0.05$ (two-sided) on the null hypothesis of no difference between the treatment groups.

Primary endpoint: The primary efficacy analysis compared the change in number of urinary incontinence episodes per day from baseline to Endpoint (Week 12/LOCF) between OTG and placebo groups. The number of urinary incontinence episodes was obtained from a 3-day urinary diary. The average number of episodes per day was calculated by dividing the total number of incontinence episodes recorded on the 3-day urinary diary by the number of days with data recorded in the diary. The primary efficacy analysis was analyzed for the mITT population with LOCF imputation for missing data. A secondary efficacy analysis was conducted on the ITT population.

Secondary endpoints: Analyses of secondary endpoints compared the change in average daily urinary frequency, nocturia, urine volume per void, IIQ domain scores and total score, and KHQ domain scores from baseline to Endpoint (Week 12 (LOCF) between treatment groups. The analysis of secondary endpoints was performed using the mITT population.

The analyses for the primary and secondary efficacy parameters were also repeated for the Evaluable population.

Pharmacokinetic Analysis:
Plasma concentration data for oxybutynin, DEO, and the ratio of DEO to oxybutynin were summarized by visit for the active treatment group using descriptive statistics for the mITT population. Simple linear regression was used to determine if there was a linear relationship between the change from baseline in urinary incontinence episodes, average daily urinary frequency, and urine volume per void and plasma concentrations; age and plasma concentrations; and weight and plasma concentrations.

Reviewer's comment*: The Division agreed to the final Statistical Analysis Plan for OG05009 in a letter dated September 20, 2007. There were no changes to the conduct or planned analyses of OG05009.*

6.1.4 Efficacy Findings of Study OG05009

The study was conducted at 76 sites throughout the U.S., with study sites enrolling from 4 to 35 patients. The original protocol was dated September 8, 2005, and one amendment to the protocol was dated June 28, 2006. The final protocol was dated June 28, 2006. The first patient visit occurred on June 12, 2006, and the last patient visit occurred on May 17, 2007. The database was locked on August 23, 2007, and the final study report was dated December 21, 2007.

6.1.4.1 Subject Disposition

Double-blind period: A total 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 patients (11%) discontinued prematurely, primarily due to an adverse event (32 patients [4.1%]), patient's decision to withdraw or inability to participate further (30 patients [3.8%]), and lost to follow-up (17 patients [2.2%]). More OTG-exposed patients discontinued because of an adverse event, whereas more placebo

patients discontinued because of patient refusal/inability to participate further. The distribution of other reasons for discontinuation was comparable between the 2 treatment groups. See Table 12.

Table 12: 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

Open-label safety extension: Of the 701 patients who completed the double-blind period, 216 entered the open-label safety extension from 24 selected study sites. Of the 216 patients, 175 (81%) completed the 14-week safety extension. Forty-one patients (19%) discontinued prematurely, primarily due to patient refusal/inability to participate further (23 patients, 10.6%) and an adverse event (15 patients, 6.9%). Table 14 summarizes the disposition of the patients in the safety extension period by randomized treatment group in the double-blind period. At the completion of the open-label extension, patients randomized to placebo in the DB period who entered the safety extension ("Double-Blind Placebo") received a maximum of 14 weeks of active treatment, and those randomized to OTG in the DB period who entered the safety extension (Double-Blind OTG) received a maximum of 26 weeks of active treatment. The subject disposition and the distribution of reasons for premature discontinuation were similar between these 2 groups in the open-label period. See Table 13.

Table 13: Subject Disposition in the Open-Label Safety Extension

	Double-Blind Placebo N=107 n (%)	**Double-Blind OTG** N=109 n (%)	**Overall** N=216 n (%)
Completed	87 (81.3)	88 (80.7)	175 (81)
Discontinued	20 (18.7)	21 (19.2)	41 (21)
Discontinuation due to:			
* Adverse event	8 (7.5)	7 (6.4)	15 (6.9)
* Patient refusal/inability to participate further	11 (10.3)	12 (11.0)	23 (10.6)
* Lost to follow-up	1 (0.9)	0 (0.0)	1 (0.5)
* Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
* Investigator recommendation	0 (0.0)	0 (0.0)	0 (0.0)
* Other	0 (0.0)	2 (1.8)	2 (0.9)

Source: Study Report, Table 10-2, p. 52

6.1.4.2 Misrandomization, Protocol Violations and Compliance

Misrandomization: Nine patients were randomized out of sequence, six of whom received a treatment different from the randomized treatment. Four patients (13218, 14121, 16517, and 17214) received

placebo when they should have received active treatment, and two patients (16518 and 17205) received active treatment when they should have received placebo.

Protocol Violations: A total of 47 patients had a total of 47 major protocol violations, all of which occurred during the double-blind period. The most common violations included not withdrawing patients who had withdrawal criteria (25 patients, mostly due to a urinary tract infection) and a significant lack of compliance (14 patients).

***Reviewer's comment**: Overall, 23 placebo patients and 24 OTG patients had a major protocol violation.*

Compliance: Compliance was measured as the ratio of the number of sachets used divided by the number expected to be used. Over the 12-week double-blind period, the mean overall treatment compliance was approximately 90% for each treatment group. During the open-label period, the mean compliance was approximately 89% in each treatment group (double-blind placebo and double-blind OTG). One patient was withdrawn from the study (Patient 12603-OTG) because of significant lack of compliance, and 14 patients were excluded from the Evaluable population due to compliance < 50%.

***Reviewer's comment:** A review of the compliance dataset indicated that, during the double-blind period, 33 patients on active treatment and 29 patients on placebo had at least one visit where compliance rate was < 50%. In the OTG group, there were 47 visits in 33 patients where compliance was < 50%; in the placebo group, there were 50 visits in 29 patients where compliance was < 50%. Overall, the incidence of non-compliance was similar between the 2 treatment arms during the double-blind period and therefore, should not alter efficacy results.*

6.1.4.3 Data Sets Analyzed

Three patient populations were used in the efficacy analysis (mITT, ITT, and Evaluable). Both the mITT and the ITT populations included 789 patients, and the Evaluable population included 663 patients (see Table 14). The ITT population was the same as the mITT population, except data from 9 patients randomized out of sequence were summarized according to the randomized treatment in the former. Patients excluded from the Evaluable population included the 85 patients (11%) who discontinued before completing 12 weeks of treatment, 33 patients (4%) who had major protocol deviations, and 8 patients (1%) who did not provide data for the primary endpoint at Week 12.

Table 14: Analysis Populations by Treatment

Population	Placebo	OTG	Overall
mITT	400	389	789
ITT	400	389	789
Evaluable	338	325	663

Source: Study report, Table 11-1, p. 54

6.1.4.4 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the 2 treatment groups in the double-blind period of Study OG05009 are summarized in Table 15. The majority of patients were non-Hispanic (94-95%), White (84-89%) females (88-91%). The mean age for both treatment groups was 59 years. Approximately 35% of patients in each treatment group were ≥ 65 years old. Mean duration of incontinence at study entry was 97.4 months (8.1 years) and 107 months (8.9 years) for the placebo and OTG groups, respectively. The median duration of incontinence was 60.0 months (5 years) for both groups. Approximately 27% of placebo patients and 23% of OTG patients have previously or currently

been treated with pharmacologic treatment for OAB. Approximately 2% of patients in each treatment group had neurogenic causes of urinary incontinence.

Table 15: 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

The demographics and baseline characteristics of patients enrolled in the open-label period were similar to those of the double-blind period. 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 with a mean BMI of 31 kg/m^2 and a mean duration of incontinence of 107 months. Approximately 27% of patients have had previous medical treatment for OAB.

Reviewer's comment: *No significant differences in patient characteristics were noted between placebo and OTG-exposed patients or between patients enrolled in the double-blind and those participating in the open-label periods.*

To assess whether patients who withdrew prematurely ("non-completers") differed from those who completed the study ("completers"), this reviewer independently analyzed some key baseline characteristics that could impact study results (Table 16). Compared to the "completers," a slightly greater proportion of non-completers were males, and non-completers also had slightly higher mean number of daily incontinence episodes per day. This reviewer does not anticipate that these differences would bias study results one way or another.

Table 16: Baseline Characteristics of Completers versus Non-Completers (MO's Analysis)

Baseline characteristics	Completers N=701	Non-completers N=88
Age mean (SD) (years)	59.5 (11.9)	58.5 (15.5)
Geriatric status (≥ 65 years old) (%)	36%	36%
Males (%)	10%	15%
# daily incontinence episodes mean (SD)	5.3 (3.1)	5.9 (4.4)

6.1.4.5 Efficacy Results

Primary endpoint: *Change from baseline to Endpoint (Week 12, LOCF) in the number of urinary incontinence episodes per day*

The primary comparison of interest was OTG treatment compared to placebo for the change from baseline to Endpoint in number of urinary incontinence episodes per day. The mean (5.4) and median (4.7) number of daily incontinence episodes at baseline was identical for the 2 treatment groups. At Endpoint, the mean change from baseline incontinence episodes per day was -3.0 for the OTG group (56% improvement) and -2.5 for the placebo group (46% improvement). The mean difference between the active and placebo groups were -0.51 incontinence episodes per day (95% CI: -0.14, -0.87) and this difference was statistically significant ($p < 0.0001$). The median change from baseline in the primary endpoint was -2.7 for the OTG group and -2.0 for the placebo group. Similar results were obtained using the OC dataset. See Table 17.

Table 17: 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,-0.87)** **<0.0001***
		Placebo N=358	OTG N=348
Change from baseline to Endpoint (OC)	Mean (SD) Median p-value	-2.6 (3.1) -2.3	-3.0 (2.8) -2.7 0.0004

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

Reviewer's comment: *There was a wide variability in the number of daily urinary incontinence episodes at baseline and in the changes from baseline, as seen in other OAB phase 3 clinical trials.*

The sponsor used the ITT population in the secondary analysis of the primary endpoint. The results were similar to those obtained with the mITT population (Table 18).

Table 18: Urinary Incontinence Episodes per Day (ITT)

	Statistic	Placebo N = 398	OTG N = 391
Baseline	Mean (SD) Median	5.3 (3.3) 4.7	5.4 (3.3) 4.7
Change from baseline to Endpoint (LOCF)	Mean (SD) Median p-value	-2.4 (3.0) -2.0	-3.0 (2.8) -2.7 <0.0001*
		Placebo N=356	OTG N=350
Change from baseline to Endpoint (OC)	Mean (SD) Median p-value	-2.6 (3.0) -2.3	-3.0 (2.8) -2.7 0.0003

*Versus placebo comparing least squares adjusted means
Source: Study report, Tables 14.2.1-3, 4, p. 181-2

***Reviewer's comment**: Ideally, the ITT population should have been the primary analysis population. However, the efficacy results using the mITT and ITT populations were almost identical. Overall, the efficacy results are consistently positive using different analysis populations and datasets. The efficacy analysis of the primary endpoint using the Evaluable population produced results similar to those obtained with the mITT and ITT populations.*

***Reviewer's comment:** The treatment effect of OTG 10% is modest (mean treatment difference -0.5 episode/day) but it is comparable to those observed with other approved OAB products, including Oxytrol TDS. See Table 19. The placebo response was significant in OG05009 (46% improvement from baseline), as seen in other clinical OAB trials. Control arms in randomized trials of urinary incontinence treatment demonstrate variable but real placebo responses, with rates ranging from 30-40% or higher.*[4]

Table 19: Treatment Effect of Other OAB Products

Products	Placebo	Drug	Treatment Effect
Oxytrol TDS (oxybutynin) Trial 1: # incontinence episodes per day Mean (SD) Baseline Mean (SD) change from baseline Trial 2: # incontinence episodes per week Mean (SD) Baseline Mean (SD) change from baseline	 5.0 (3.2) -2.1 (3.0) 37.7 (24.0) -19.2 (21.4)	 4.7 (2.9) -2.9 (3.0) 34.3 (18.2) -21.0 (17.1)	 ***Mean: -0.8 episode/ day*** ***Mean: -1.8 episodes/week***
Detrol LA (tolterodine) # incontinence episodes per week Mean Baseline Mean change from baseline	 23.3 -6.9	 22.1 -11.8	 ***Mean: -4.8 episodes/week or -0.69 episode/day***
Enablex (darifenacin) 7.5 mg* # incontinence episodes per week Median Baseline Median change from baseline	 16 -6 to -9	 16 -8 to -9	 ***Median: -1.5 to -2.8 episodes/week***

*Lowest effective dose
Source: Oxytrol TDS, Detrol LA, Enablex product labels

Compared to placebo, the improvement (decrease) in urinary incontinence episodes with OTG treatment was statistically significant beginning at the Week 4 visit and was maintained throughout the double-blind period (see Table 20).

Table 20: Change from Baseline in Daily Urinary Incontinence Episodes by Visit (mITT, OC)

Weeks post-randomization	Statistic	Placebo	OTG
1	Mean (SD)	-1.8 (2.6)	-2.0 (2.4)
	p-value		0.18*
	n	390	384
4	Mean (SD)	-2.3 (2.9)	-2.7 (2.6)
	p-value		0.0004*
	n	374	366
8	Mean (SD)	-2.5 (2.9)	-3.0 (2.6)
	p-value		0.0002*
	n	359	354
12	Mean (SD)	-2.6 (3.1)	-3.0 (2.8)
	p-value		0.0004*
	n	358	348

*Versus placebo comparing least squares adjusted means
Source: Study report, Table 14-2.1-2, p. 178

The sponsor analyzed the results of an exploratory endpoint: "complete continence" during the double-blind period. This endpoint was defined as the absence of any incontinence episode in a 3-day urinary diary. At Endpoint (LOCF), 69 placebo patients (17.3%) and 108 OTG patients (27.8%) achieved "complete continence." Furthermore, 96 placebo patients (24.0%) and 135 OTG patients (34.7%) achieved "complete continence" at any visit during the double-blind period. Similar results were obtained using the ITT population. See Table 21.

Table 21: Number and Percentage of Patients Achieving Continence (mITT)

Weeks Post-randomization	# patients evaluated Placebo/OTG	Placebo n (%)	OTG n (%)
1 (OC)	390/384	16 (4.1)	25 (6.5)
4 (OC)	374/366	44 (11.8)	74 (20.2)
8 (OC)	359/354	51 (14.2)	89 (25.1)
12 (OC)	358/348	66 (18.4)	103 (29.6)
Endpoint (LOCF)	400/389	69 (17.3)	108 (27.8)
At any visit	400/389	96 (24.0)	135 (34.7)

Source: Study report, Table 14.2.5-1, p. 329

***Reviewer's comment**: In the double-blind, placebo-controlled, active controlled phase 3 trial of Oxytrol TDS (3.9 mg/day), 30% and 22% patients receiving Oxytrol and placebo, respectively, achieved continence. These results are similar to those of OG05009.*

***Reviewer's comment**: "Complete continence" defined by the sponsor meant no urinary incontinence in the 3-day period that the patients were recording the urinary diary data, and not a cure of urinary incontinence. The proportion of patients experiencing "complete continence" at any visit was impressive, both for placebo (1/4) and active treatment (1/3), given the severity of the patients' baseline*

urinary incontinence. The treatment effect of OTG on this endpoint was approximately 10%, which is modest. It is unclear if these extreme "responders" skewed the results for the primary efficacy endpoint.

This reviewer analyzed urinary diary dataset (AF-DIARY.XPT) to further explore details of the complete continence data:

- *There appeared to be a modest treatment effect based on the number of urinary diary entries that were reported as "complete continence." Out of a total of 4511 diary entries, 645 (or 14%) were recorded as "complete continence." In the OTG group, 399 of 2230 entries (or 18%) were reported as "complete continence" compared to 246 of 2281 (or 11%) in the placebo group.*
- *Patients who reported "complete continence" were not clustered at any group of study sites. Sixty-six (66) out of 76 sites had at least one record of "complete continence" entry. Twenty-eight sites had ≥ 10 entries of "complete continence." These 28 sites had 70% of the "complete continence" entries (450 of 645 entries). The following 5 sites had ≥ 20 entries of "complete continence": 135 (34 entries), 155 (31 entries), 128 (27 entries), 166 (22 entries), and 130 (21 entries).*
- *It appears that the patients who had at least one diary entry of "complete continence" had less severe urinary incontinence at baseline compared to those who did not (mean [SD] number of baseline incontinence episodes of 3.8 [2.5] versus 5.6 [3.2]).*

Secondary Endpoints:

a. *Change from baseline to Endpoint (Week 12, LOCF) in daily urinary frequency*

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). The median number of daily urinary frequency decreased by 2.7 in the OTG group compared to the median decrease of 1.7 in the placebo group. See Table 22. Compared to placebo, the improvement (decrease) in daily urinary frequency with OTG treatment was statistically significant beginning at the Week 4 visit and was maintained throughout the double-blind period. Similar results were obtained using the ITT and Evaluable analysis populations.

Table 22: 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

***Reviewer's comment**: Treatment benefit on urinary frequency is clinically important as approximately 2/3 of OAB patients do not have urinary incontinence but only have excessive urinary frequency (and urgency). The mean treatment effect of OTG on urinary frequency (decrease of 0.5 micturition per day) is modest, although it is similar to that observed with Oxytrol TDS. For example, compared to placebo, the mean improvement in urinary frequency with Oxytrol TDS treatment was a decrease of 0.5 to 0.6 micturitions per day and the median improvement was a decrease of 1.0 micturition per day.*

b. *Change from baseline to Endpoint (Week 12, LOCF) in average volume voided per micturition*

The mean (approximately 165 mL) and median (160 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 +17 mL and this difference was statistically significant (p = 0.0018). The median change from baseline in the same efficacy parameter was 0.0 mL for placebo and +11.5 mL for OTG. See Table 23. Compared to placebo, a statistically significant improvement in the average volume voided per micturition with OTG treatment was noted beginning at Week 1 and was maintained throughout the double-blind period. Similar results were obtained using the ITT and Evaluable analysis populations.

Table 23: Average Volume Voided per Void (mITT, LOCF)

	Statistic	**Placebo N = 400**	**OTG N = 389**
Baseline	Mean (SD) Median	167.9 (68.4) 160.6	163.4 (65.9) 160.1
Change from baseline to Endpoint	**Mean (SD)** Median p-value	**3.8 (53.8)** 0.0	**21.0 (65.3)** 11.5 **0.0018***

*Versus placebo comparing least squares adjusted means
Source: Study report, Table 11-8, p. 63

***Reviewer's comment**: Treatment effect on the average volume voided per micturition is a commonly used pharmacodynamic endpoint to assess the anticholinergic effect on bladder storage capacity. It is unlikely, however, that a mean increase of 17 mL in bladder storage is clinically meaningful to an OAB patient.*

The treatment effect of OTG 10% on the average voided volume per micturition is similar to that of Oxytrol TDS. Compared to placebo, the mean increase in the average volume per void with Oxytrol TDS (3.9 mg/day) treatment was approximately +20 mL.

c. *Change from baseline to Endpoint in daily nocturia events*

There were no differences between placebo and OTG treatment in the number of nocturia events at baseline (mean [SD] of 2.5 [1.7]) or at Endpoint (mean [SD] of 1.7 [1.5]).

d. *Change from baseline to Endpoint in the Quality of Life instruments*

Incontinence Impact Questionnaire (IIQ)
During the double-blind treatment period, OTG treatment demonstrated a statistically significant improvement (p = 0.0005) in the IIQ total score when compare to placebo. At baseline, the mean IIQ total score for the mITT OTG group was 183.8, which was slightly higher than that of placebo (170.0). At Endpoint, the mean change from baseline for the OTG group was -72.1 (SD 80.0) or a 39% improvement; the mean change from baseline for placebo was -49.5 (SD 76.6) or a 29% improvement. Consistent and statistically significant improvements were also observed in all subscales at Endpoint. See Table 24.

Table 24: Baseline and Change from Baseline to Endpoint in IIQ (mITT)

IIQ	Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
IIQ Total Score			
* Placebo+	170.0 (88.6)	-49.5 (77.0)	
* OTG+	183.8 (93.9)	-72.1 (80.0)	0.0005
IIQ Subscales			
Travel			
* Placebo	51.4 (27.1)	-15.1 (24.8)	
* OTG	54.9 (27.7)	-20.9 (25.6)	0.0068
Physical Activity			
* Placebo	41.9 (24.0)	-13.0 (21.7)	
* OTG	44.8 (25.1)	-18.0 (23.2)	0.0078
Social Relationships			
* Placebo	32.9 (23.5)	-9.7 (19.3)	
* OTG	37.3 (25.5)	-15.2 (20.1)	0.0019
Emotional Health			
* Placebo	43.9 (24.1)	-11.8 (20.1)	
* OTG	46.9 (25.4)	-18.1 (22.0)	0.0002

+ Placebo N=400; OTG N=389
Source: Study report, Table 11-10, p. 65

King's Health Questionnaire (KHQ)

During the double-blind treatment period, OTG treatment demonstrated a statistically significant improvement ($p \leq 0.05$) in the domains of Incontinence Impact, Symptom Severity, Role Limitations, Personal Relationships, Sleep and Energy, and Severity (Coping) Measures of the KHQ compared to placebo. OTG treatment did not demonstrate statistically significant improvement from baseline to Endpoint in the domains of General Health Perceptions, Physical Limitations, Social Limitations, or Emotions compared to placebo. See Table 25.

Table 25: Baseline and Change from Baseline to Endpoint in KHQ (mITT)

KHQ Domains	Baseline Mean (SD)	Change from baseline Mean (SD)	P-value
Incontinence Impact			
* Placebo+	78.3 (23.7)	-21.3 (27.1)	
* OTG+	79.9 (23.2)	-27.9 (30.0)	0.0023
Symptom Severity			
* Placebo+	18.2 (18.2)	-15.8 (21.8)	
* OTG+	18.6 (18.4)	-20.6 (22.9)	0.0024
Role Limitations			
* Placebo	56.1 (28.3)	-21.3 (27.2)	
* OTG	59.1 (28.4)	-27.1 (29.2)	0.01
Personal Relationships			
* Placebo	21.0 (27.5)	-6.2 (20.0)	
* OTG	25.3 (31.1)	-11.2 (25.0)	0.05
Sleep and Energy			
* Placebo	57.0 (26.0)	-10.3 (22.4)	
* OTG	60.0 (26)	-15.6 (24.2)	0.006
Severity (Coping) Measures			
* Placebo	58.7 (24.6)	-11.1 (19.2)	
* OTG	60.3 (23.9)	-15.3 (21.4)	0.006
General Health Perception			
* Placebo	21.3 (16.8)	0.1 (11.9)	
* OTG	21.4 (17.3)	0.4 (12.2)	0.65
Physical Limitations			
* Placebo	54.8 (29.9)	-16.8 (28.1)	
* OTG	55.7 (29.7)	-20.2 (30.0)	0.11
Social Limitations			
* Placebo	29.6 (26.5)	-10.3 (23.5)	
* OTG	29.9 (28.0)	-11.5 (24.4)	0.45
Emotions			
* Placebo	35.1 (27.6)	-8.4 (24.9)	
* OTG	36.1 (27.1)	-11.7 (24.6)	0.06

+ Placebo N=400; OTG N=389
Source: Study report, Table 11-10, p. 65

***Reviewer's comment**: The IIQ and KQH are considered exploratory endpoints and would not support labeling claims. The sponsor submitted published literature references to support the use of these 2 instruments in measuring treatment benefits in the target population. A review of the submitted literature revealed several key deficiencies of these 2 instruments that may render them inadequate measurement tools for clinical efficacy in OAB registration trials. A few examples of these deficiencies follow:*

IIQ:

- *Study population: The instrument was developed in a focus group consisting primarily of women with genuine stress incontinence who were recruited from a single region in the U.S (Southeast). This patient population may not be generalizable to the study population of OG05009 who primarily experienced urinary urge incontinence.*

- *Item generation and development: There is no evidence of cognitive debriefing to ensure that the instrument is understandable and relevant to the target population.*
- *Psychometric validation: There is no evaluation of test-retest validity. The results of construct validity are marginal given the minimal to modest correlation between the IIQ and other comparators (other PRO's, number of urinary incontinence episodes).*

KHQ:

- *Study population: Unclear if the population in which the instrument was developed for is sufficiently similar to the study population of OG05009.*
- *Psychometric properties: The instrument had domains that did not appear to be relevant to the OAB population (e.g., personal relationship domain, social limitation domain), the instrument items had floor and ceiling effects, and the various domains correlated minimally with other PRO's and clinical endpoints (e.g., number of urinary incontinence episodes).*

The changes in total/domain scores that represent a meaningful clinical treatment are unknown for both of these PRO instruments. Statistical significance is not sufficient to demonstrate a meaningful clinical benefit. Furthermore, simultaneous statistical testing of multiple domains and total scores without adjusting for multiplicity can lead to false positive conclusions.

6.1.6 Efficacy Conclusions

1. The results of the primary 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. The improvement in the urinary incontinence episodes per day is modest but similar to other approved OAB products. The improvements in the key secondary endpoints are modest but consistent with the finding of the primary endpoint.
2. Compared to placebo, OTG treatment resulted in improvement in the primary endpoint from Week 4 to Week 12.
3. The improvement in efficacy parameters was consistent when analyzed by different analysis populations and datasets.
4. The results of the IIQ and KHQ are considered exploratory and will not support labeling claims.

7 INTEGRATED REVIEW OF SAFETY

7.1 METHODS AND FINDINGS

Methods

The following sources were reviewed for safety assessment:

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 adequate and well-controlled 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. Detailed reviews of these studies are presented in Appendix 10.1.2-10.1.4.
3. Annual reports of Oxytrol TDS and IND 67,126 and the 120-day Safety Update.

4. Published literature and approved OAB product labels

***Reviewer's comment**: For clarification purposes, "integrated" studies were those that were included in the Integrated Summary of Safety (ISS) and "non-integrated" studies were those that were not included in the ISS.*

Extent of Exposure
In total, the NDA 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), 216 healthy subjects in the integrated phase 1 studies, and 296 healthy subjects in the non-integrated phase 1 studies.

Integrated Phase 3 study: Overall, 496 patients (389 randomized to active OTG in the double-blind [DB] period + 107 randomized to placebo in the DB period and who received active OTG during the open-label [OL] 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; 85 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 active OTG group. In the open-label period, the mean exposure to active OTG was 89.9 days (range 1-142 days).

There were no significant differences in exposure with regards to gender, race, or geriatric status in the phase 3 study.

***Reviewer's comment**: In the phase 3 study, exposures are categorized by treatment duration of **<12 weeks** and **≥12 weeks**. The **≥ 12 weeks** group include only patients who were randomized to active OTG treatment in the double-blind period and who also entered the open-label period (N=109). The **<12 weeks** group includes patients who received active treatment in the double-blind and did not participate in the open-label study and patients who randomized to placebo in the double-blind period and enrolled in the 14-week open-label extension (even though these patients may have received 14 weeks of active OTG treatment in the open-label extension).*

If one were to evaluate exposure based on the actual duration of treatment (and not by the sponsor's method of < 12 weeks and ≥ 12 weeks described in the paragraph above), then 431 of the 496 patients exposed to at least one dose of 1 g 10% OTG received at least 12 weeks of treatment.

Integrated Phase 1 studies: In the integrated phase 1 studies, 118 subjects were exposed to 1 g 10% OTG, 116 subjects to 3 g 4.4% OTG, 41 subjects to 1 g 13.2% OTG, and 21 subjects to 3 g 10% OTG. Exposure in these studies ranged from 1 to 42 days.

Non-integrated studies: In the cumulative irritation study (OG05003), 45 healthy subjects received daily applications of 1 g 10% OTG for 21 days. In the skin sensitization study (OG05004), 225 healthy subjects received 0.5 g 10% OTG three times a week for 3 weeks followed by a single 24-hour challenge application. In the transference study (OG06007), 26 healthy subjects received one dose of 1g 10% OTG.

***Reviewer's comment**:*
1. *It appears that 1008 subjects (496 OAB patients in the phase 3 study + 216 healthy subjects in the 10 integrated phase 1 studies + 296 healthy subjects in the 3 non-integrated studies), and not 1033 as stated by the sponsor, were exposed to active OTG. The 1033 number may have included the 26*

untreated partners in the transference study (OG06007) who could be exposed to OTG via skin transfer from their treated partners.

2. *In total, 614 subjects were exposed to at least one dose of the to-be-marketed dose/formulation 1 g 10% OTG, and 85 patients were exposed to 6 months of active treatment. Although these exposure numbers are less than those recommended by the ICH guidelines for a chronically administered drug, the safety profile of systemic oxybutynin is well-known. The sponsor fulfilled the Division's request that at least 50 patients receive 6 months of OTG, and the safety exposure of OTG is adequate to evaluate skin safety.*
3. *One hundred seventy-eight (178) subjects were exposed to doses higher than the to-be-marketed dose (100 mg oxybutynin), although 80% of these subjects were exposed only to single doses.*
4. *Although safety data from 10 phase 1 studies and 1 phase 3 study were summarized in the Integrated Summary of Safety (ISS), the sponsor presented the data of the integrated phase 1 studies separately from those of the phase 3 study. This approach is acceptable because the study methodology and patient population differed significantly between the phase 1 and phase 3 studies.*
5. *Overall, the quantity and duration of patient exposure was adequate for an oxybutynin product.*

Protocol defined safety assessments

Key safety assessments included treatment-emergent adverse events, skin tolerability, laboratory tests, physical examination, vital signs, and electrocardiograms. Post-void residual urine volume was measured only in the double-blind period of Study OG05009. Skin tolerability to OTG was assessed in all 11 integrated studies by visual inspection of the application area at various time points post-application. Hematology, serum chemistry, and urinalysis were performed at baseline and at study exit only in the phase 3 study (OG05009). No clinical laboratory test results were summarized for healthy volunteer subjects because laboratory assessments were performed only at baseline for eligibility purposes.

Demographics and baseline characteristics

The sponsor did not pool the demographic and other baseline characteristics of the subjects in the 11 integrated safety studies. Instead, the sponsor presented the demographic and baseline characteristics for 3 different populations from the 11 integrated safety studies as follows: 1) Healthy Volunteers, 2) Controlled Study in OAB Patients, and 3) Controlled and Uncontrolled Study in OAB Patients. The data for the 3 different populations were also presented according to the total daily dose and formulation.

In Study OG05009, the 2 treatment groups were similar with respect to age (mean 59 years), geriatric status (35-37% were ≥ 65 years of age), race (84-90% White), BMI (mean 31 kg/m^2), and gender distribution (88-90% female). The baseline characteristics of patients who received active treatment for < 12 weeks were similar to those who received ≥ 12 weeks of treatment. Subjects in the integrated phase 1 studies consisted of an approximately equal number of healthy male and females, most of whom were White (90%), with an average age of 26 years (none were ≥ 65 years old), and a mean BMI of 24 kg/m^2. All 322 subjects enrolled in the non-integrated studies were healthy subjects, between the ages of 18 and 65 years, and 61% were females.

Summary of overall safety findings of the ISS

An overview of the incidences of adverse events and adverse reactions (drug-related AE's) are presented for the double-blind period of the phase 3 study, open-label period of the phase 3 study, for duration of active OTG treatment, and for the integrated phase 1 studies in Tables 26, 27, 28 and 29, respectively.

Table 26: Summary of AE's in the Double-Blind Phase 3 Study

Assessment	OTG N=389 n (%)	Placebo N=400 n (%)
Any adverse event Drug-related Severe	221 (57) 73 (19) 16 (4)	193 (48) 45 (11) 16 (4)
Serious AE (no deaths)	7 (1.8)	10 (2.5)
Discontinuation Drug-related	19 (4.9) 7 (1.8)	13 (3.3) 7 (1.8)
Application site reactions Leading to discontinuation	21 (5.4) 3 (0.8)	4 (1) 1 (0.3)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 13, p. 28

Reviewer's comment: *Over a 12-week treatment period, the incidences of treatment-emergent AE's and AR's were higher in the OTG group than in the placebo group. Although more discontinuations due to an adverse event occurred in the OTG group, the incidence of discontinuation due to an adverse reaction was similar between the OTG and placebo groups. More patients on placebo than on active treatment experienced a serious adverse event (SAE), although none of the SAE's was considered treatment-related.*

Table 27: Summary of AE's in the Open-Label Phase 3 Study

Assessment	OTG N=216 n (%)
Any adverse event Drug-related Severe	97 (45) 22 (10) 9 (4.2)
Serious AE	0
Discontinuation Drug-related	15 (6.9) 11 (5.1)
Application site reactions Leading to discontinuation	13 (6.0) 9 (4.2)

Source: Study report, Table 12-3, p. 79

Table 28: Summary of AE's in Phase 3 Study by Duration of Active OTG Treatment

Assessment	OTG < 12 weeks* N=387 Mean exposure = 82.0 days n (%)	OTG ≥ 12 weeks** N=109 Mean exposure = 177.3 days n (%)
Any adverse event Drug-related Severe	218 (56) 69 (18) 18 (5)	70 (64) 22 (20) 6 (6)
Serious AE (no deaths)	6 (1.6)	1 (0.9)
Discontinuation Drug-related	27 (7) 13 (3.4)	7 (6.4) 5 (4.6)
Application site reactions Leading to discontinuation	24 (6.2) 8 (2.1)	9 (8.3) 4 (3.7)

*<12 weeks=patients randomized to OTG in DB period but did not enter OL period & patients randomized to placebo in DB period and entered the OL period
**≥12 weeks=patients randomized to OTG in DB period and entered the OL period
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 14, p. 29

Reviewer's comment: *The incidences of application site reactions and discontinuation due to application site reactions were higher in patients treated ≥ 12 weeks (8.3%) than those treated < 12 weeks (6.2%) with OTG.*

Table 29: Summary of AE's in Integrated Phase 1 Studies

Assessment	1 g 10% OTG[1] N=118 n (%)	3 g 10% OTG[1] N=21 n (%)	Other OTG**[1] N=116 n (%)	Oxytrol [1] N=43 n (%)
Any adverse event Drug-related Severe	36 (31) 29 (25) 0	2 (10) 2 (10) 0	38 (33) 27 (23) 0	15 (35) 15 (35) 0
Application site reactions Leading to discontinuation	2 (1.7) 0	0 0	4 (3.4) 0	13 (30) 0
Serious AE	0	0	0	0
Discontinuation Drug-related	2 (1.7) 0	0 0	1 (1) 0	0 0

*Other OTG = 3 g 4.4% and 1 g 13.2% dose/formulation
[1]Mean duration of exposure (days): 1 g 10% OTG (23); 3 g 10% OTG (1); Other OTG (3); Oxytrol (11)
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 12, p. 27

Reviewer's comment: *No clinically significant or unexpected differences in safety were noted between different groups of comparison.*

7.1.1 Deaths

One death occurred in the entire safety database. A 54 year-old female subject (1039) 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, gastrointestinal [GI] bleed), according to a

medical examiner's autopsy report. The death was not considered to be treatment-related, and this reviewer agrees.

7.1.2 Other Serious Adverse Events

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 phase 3 study. Serious adverse events 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.

Reviewer's comment: *This reviewer reviewed all SAE case narratives and did not consider any SAE to be treatment-related.*

7.1.3 Dropouts and Other Significant Adverse Events

Phase 3 study (DB and OL periods): Overall, 47 of 789 patients (6.0%) withdrew from the study due to an adverse event. These 47 patients included 13 placebo-treated patients (13 of 400, or 3.3%) and 34 OTG-treated patients (34 of 496, or 6.9%). Of those who discontinued, 25 patients did so because of a treatment-related AE (7 placebo patients [1.8%] and 18 OTG patients [3.6%]). The most common drug-related AE's leading to premature discontinuation were application site reactions (12 OTG patients or 2.4%, 1 placebo patient or 0.25%), which accounted for approximately 50% of the patients who discontinued prematurely. These application site reactions included rash, pruritus, pustules, erythema, dryness, discoloration, hives, and papules and ranged from mild to severe in severity. Three patients (3/496 or 0.6%) reported the 5 severe application site reactions (11815-erythema x 2, 13528-pruritus, and 16601-urticaria, dermatitis) which led to the patients' discontinuation from the open-label extension.

- 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 was headache (4 patients in OTG [1%], 5 in placebo [1.25%]), followed by application site reactions (3 patient in OTG group [0.8%], 1 patient in 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 pruritus (4 patients) dermatitis (3 patients), dryness (3 patients), erythema (2 patients), pustules (2 patients), discoloration (1 patient), and papules (1 patient).
- Duration of active OTG treatment (< 12 weeks, ≥ 12 weeks): The discontinuation rates due to an AE's were similar for patients exposed to < 12 weeks (7.0%) and those exposed ≥ 12 weeks (6.4%). The discontinuation rates due to an adverse reaction was slightly higher in patients exposed to ≥ 12 weeks (4.6%) compared to those exposed < 12 weeks (3.4%). 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%).

***Reviewer's comment**: Among patients who received at least one dose of OTG treatment in the phase 3 study, there was a notable difference in the incidence of discontinuation due to application site reactions in the double-blind period (3 patients, 0.8%) compared to the open-label period (9 patients, 4.2%). During the open-label period, 5 patients randomized to placebo and 4 patients randomized to active OTG during the double-blind period discontinued because of application site reactions. Therefore, it appears that application site reactions significant enough to lead to study discontinuation can occur anytime during the course of OTG treatment. The average (SD) interval between initiation of active OTG treatment and onset of skin reaction that led to withdrawal was 59 (54) days (range 1-155 days).*

According to the sponsor, skin erythema scores for patients who discontinued because of application site AE's were "most commonly indicative of no erythema," which suggested that lack of erythema does not necessarily indicate acceptable skin tolerability. Furthermore, it was unclear if some of the significant application site reactions could be skin hypersensitivity reactions.

This reviewer reviewed the line listing of "Adverse Events Leading to Premature Discontinuation" and case narratives for all discontinuations in the double-blind and open-label periods of the phase 3 study (Study Report, Listing 14.3.2-3, Amendment 0004 dated August 27, 2008). In the double-blind period, 7 OTG patients discontinued due to adverse events considered by the investigator to be treatment-related (application site dermatitis, headache x 2, application site pruritus, dry skin/dry eyes/dry mouth, application site pruritus/dermatitis/headache, application site pustules, and constipation). There were two additional discontinuations in the active group that this reviewer considered to possibly be drug-related: patient 11904 discontinued because of dizziness and patient 12402 discontinued because of headache, although the investigator did not considered these AE's to be drug-related. In the double-blind and open-label phase 3 study, adverse reactions leading to premature discontinuation reported in > 1 OTG-treated patient are summarized in Table 30. Other adverse reactions leading to premature discontinuation among patients who received at least one dose of active OTG were (1 patient each): hypertonic bladder, dizziness, abdominal distension, hemorrhoids, abnormal LFT's, dry skin, dry mouth, dry eyes, application site erythema, application site discoloration, application site urticaria, and application site papules. Premature discontinuation due to anticholinergic adverse reactions was < 1%.

Table 30: **Adverse Reactions Leading to Discontinuation in Phase 3 Study (MO's Analysis)**

Preferred Term	OTG* N=496 n+ (%)	Placebo N=400 n (%)
Application site dermatitis	4 (0.8)	0
Application site pruritus	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.

Integrated phase 1 studies: 3 of 216 subjects (1.4%) discontinued due an adverse event (1 each for puncture site hematoma, urinary tract infection, and vomiting), none of which were considered related to treatment.

7.1.5 Common Adverse Events

TREATMENT-EMERGENT ADVERSE EVENTS:

- *Double-blind phase 3 study*: Adverse event rates were higher in OTG group than the placebo group (56.8% versus 48.3%). The most commonly reported AE's (>2% and greater than placebo) by MedDRA Preferred Terms were dry mouth, urinary tract infection, upper respiratory infection, dizziness, nasopharyngitis, application site pruritus, fatigue, and viral gastroenteritis. There were no significant differences in the incidence and frequency of AE's among patients ≥ 65 years old compared to younger patients.
- *Open-label phase 3 study*: The most common AE's were urinary tract infection, upper respiratory tract infection, application site dermatitis, application site pruritus, and urinalysis abnormal.
- *Duration of active OTG treatment*: Adverse events rates were slightly higher for patients treated for ≥ 12 weeks than those treated < 12 weeks (64.2% versus 56.3%).
- *Integrated phase 1 studies*: The most common AE's in the integrated phase 1 studies with the 10% OTG formulation were headache, dry mouth, dizziness, nausea, thirst, vomiting, pyrexia, and application site pruritus.

The most common AE's by Preferred Terms in the integrated phase 3 study are presented in Table 31, Table 33, and Table 34; and AE's in the integrated phase 1 studies are presented in Table 35. The AE's are discussed separately in the following order: double-blind phase 3 study, open-label phase 3 study, duration of active OTG treatment in the phase 3 study, and the integrated phase 1 studies.

Double-blind phase 3 study:

Table 31: Common Adverse Events (> 2% and > placebo) for Double-Blind Phase 3 Study

Preferred Term	1g 10% OTG N=389 n (%)	Placebo N=400 n (%)
Any AE	**221 (56.8)**	**193 (48.3)**
Dry mouth	29 (7.5)	11 (2.8)
Urinary tract infection	27 (7)	17 (4.3)
Upper respiratory tract infection	21 (5.4)	20 (5)
Dizziness	11 (2.8)	4 (1)
Nasopharyngitis	11 (2.8)	9 (2.3)
Application site pruritus	8 (2.1)	3 (0.8)
Fatigue	8 (2.1)	4 (1)
Gastroenteritis viral	8 (2.1)	7 (1.8)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 16, p. 31

Reviewer's comment: *No unexpected adverse events were noted based on the known safety profile of oxybutynin. Dry mouth, dizziness, application site pruritus, and fatigue are most likely to be treatment mediated and should be presented in product labeling. AE's of upper respiratory tract infection, nasopharyngitis, and viral gastroenteritis are unlikely to be treatment-mediated, and the higher incidences of these AE's in the OTG group are most likely due to chance. It is unclear if urinary tract infection is treatment-mediated.*

Reviewer's comment: *This reviewer conducted analyses of the various datasets (AF-AE.XPT, AF-DEMOG.XPT) to explore further details of AE findings in the double-blind phase 3 trial. The most common AE's for the overall study population in the double-blind phase 3 study are presented in Table 32. The incidences of application site reactions, dry mouth, urinary tract infection, and dizziness were notably higher in the OTG group than the placebo group. Some of the other known anticholinergic adverse effects (e.g., headaches, diarrhea, constipation) did not occur more frequently with active OTG treatment.*

Table 32: Common AE's (≥ 2%) in the Double-Blind Phase 3 Study (MO's Analysis)

Preferred Term	1g 10% OTG N=389 n (%)	Placebo N=400 n (%)	Overall N=789 n (%)
Headaches	24 (6.2)	28 (7)	52 (6.6)
Urinary tract infection	29 (7.5)	17 (4.3)	46 (5.8)
Dry mouth	29 (7.5)	12 (3)	41 (5.2)
Upper respiratory tract infection	21 (5.4)	20 (5)	41 (5.2)
Sinusitis	10 (2.6)	20 (5)	30 (3.8)
Application site reactions*	21 (5.4)	4 (1)	25 (3.2)
Diarrhea	11 (2.8)	13 (3.3)	24 (3.0)
Constipation	7 (1.8)	9 (2.3)	16 (2.0)
Dizziness	12 (3.1)	4 (1.0)	16 (2.0)

**Includes pruritus, dermatitis, papules, anesthesia, erythema, irritation, pain, and pustules*

This reviewer assessed the AE's by Preferred Terms that occurred > 1% and < 2% and greater than placebo in the OTG group. AE's meeting these criteria included: application site dermatitis (7 OTG patients [1.8%], 1 placebo patient [0.25%]) application site pruritus (6 OTG [1.5%], 5 placebo [1.2%]), peripheral edema (6 OTG [1.5%], 1 placebo [0.25%]), GGT increased (4 OTG [1%], 0 in placebo), ALT increased (4 OTG [1%], 3 in placebo). All but one case of peripheral edema was considered unrelated to treatment; the one treatment-related case was reported as "bilateral ankle edema" in a patient on active OTG. No meaningful conclusion can be drawn from these few cases of peripheral edema. The LFT elevations are discussed in detail in the "Laboratory" section of this safety review.

Because of known anticholinergic effects on the central nervous system (CNS), this reviewer evaluated specific CNS AE's by Preferred Terms. Compared to placebo, active OTG treatment was associated with higher incidences of dizziness (3% vs. 1%) and somnolence (0.8% vs. 0%). There was one case of syncope in the active OTG group; however, this AE did not appear to be treatment-related. In the double-blind phase 3 study, fifteen patients (7 OTG, 8 placebo) reported 15 AE's under the System Organ Class "Psychiatric Disorders." A majority of these AE's (12/15) were either insomnia (7) or anxiety (5). One OTG patient reported insomnia compared to 6 placebo patients. Four OTG patients (1%) reported anxiety compared to 1 placebo patient; all the anxiety AE's were mild except for one moderate AE of "anxiety secondary to pneumonia," and none led to drug discontinuation. Of the 15 AE's, 2 were considered to be treatment-related (insomnia in a placebo patient, anxiety secondary to pneumonia in an OTG patient). This reviewer does not consider the higher incidence of anxiety in the OTG group compared to placebo to be significant enough to be labeled, because anxiety is not an uncommon condition resulting from many different causes. There were no cases of hallucination, confusion, agitation, or dementia. There were no new significant neurologic or psychiatric adverse effects with OTG treatment.

Open-label phase 3 study:

Table 33: Common Adverse Events (≥ 2%) Open-Label Phase 3 Study

Preferred Term	OTG N=216 n (%)
Any adverse event	**97 (44.9)**
Urinary tract infection	19 (8.8)
Upper respiratory tract infection	10 (4.6)
Application site dermatitis	5 (2.3)
Application site pruritus	5 (2.3)
Urinalysis abnormal	5 (2.3)

Source: Study report, Table 12-7, p. 82

Reviewer's comment: *Of the 216 patients who entered the OL period, 13 patients or 6.0%, reported at least one application site AE's.*

Duration of OTG treatment in the phase 3 study:

Table 34: Common Adverse Events (≥ 2%) by Duration of OTG Treatment in Phase 3 Study

Preferred Term	OTG < 12 weeks N=387 n (%)	OTG ≥ 12 weeks N=109 n (%)	Overall N=496 n (%)
Any AE	**218 (56.3)**	**70 (64.2)**	**288 (58)**
Urinary tract infection	34 (8.8)	10 (9.2)	44 (8.9)
Upper respiratory tract infection*	19 (5)	10 (9.2)	29 (5.8)
Headache	13 (3.4)	8 (7.3)	21 (4.2)
Nasopharyngitis*	10 (2.6)	5 (4.6)	15 (3.0)
Application site pruritus	10 (2.6)	3 (2.8)	13 (2.6)
Sinusitis*	8 (2.1)	5 (4.6)	13 (2.6)
Diarrhea	7 (1.8)	5 (4.6)	12 (2.4)
Application site dermatitis	8 (2.1)	3 (2.8)	11 (2.2)
Bronchitis*	8 (2.1)	3 (2.8)	11 (2.2)
Gastroenteritis viral*	7 (1.8)	4 (3.7)	11 (2.2)

*No cases were considered by investigator to be treatment-related
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 18, p. 32-33

Reviewer's comment: *The incidence of application site pruritus and dermatitis do not appear to increase significantly with longer duration of OTG exposure. No other adverse events, other than headache and diarrhea, increased significantly with increasing duration of use.*

Integrated phase 1 studies

Table 35: Common Adverse Events (≥ 2% in OTG group) in the Integrated Phase 1 Studies

Preferred Term	Overall OTG* N=215 N (%)	Oxytrol TDS N=43 N (%)
Any AE	**73 (34.0)**	**15 (34.9)**
Headache	29 (13.5)	1 (2.3)
Dry mouth	13 (6)	0
Dizziness	9 (4.2)	0
Nausea	10 (4.7)	1 (2.3)
Thirst	9 (4.2)	0
Vomiting	6 92.8)	0
Pyrexia	6 (2.8)	0
Application site pruritus	5 (2.3)	4 (9.3)

*Inclusive of all OTG formulations, doses, and single-dose and multiple-dose studies
Source: Module 5.3.5.3, Integrated Summary of Safety, Table 15, p. 30

Reviewer's comments: *The comparability of the integrated safety data between "overall" OTG and Oxytrol TDS is very limited due to differences in study design and scope of safety data.*

COMMON DRUG-RELATED ADVERSE EVENTS (ADVERSE REACTIONS):

- *Double blind phase 3 study:* More OTG patients reported at least one adverse reaction (AR) than placebo patients (19% versus 11%). These differences were primarily due to dry mouth (6.9% versus 2.8%) and application site reactions (5.4% versus 1%). See Table 36.
- *Open-label phase 3 study:* The most common adverse reactions were application site reactions (dermatitis, pruritus, dryness, erythema), which was reported by 13 patients (6%) and dry mouth (1.9%). See Table 37.
- *Duration of active OTG treatment (< 12 weeks, ≥ 12 weeks):* More patients treated with OTG for ≥ 12 weeks reported adverse reactions than those treated less than 12 weeks (20% versus 18%). Dry mouth, headache, and constipation occurred more commonly in patients exposed < 12 weeks of treatment than those exposed to ≥ 12 weeks of treatment. See Table 38.
- *Integrated phase 1 studies:* No unexpected AR's were observed. See Table 39.

Table 36: Common Adverse Reactions (≥ 1% in OTG group) in Double-Blind 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 pruritus	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)
Pruritus	5 (1.3)	5 (1.3)

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

Table 37: Common Adverse reactions (≥ 1%) in Open-Label Phase 3 Study

Preferred Term	OTG N=216 n (%)
Any adverse reaction	**22 (10.2)**
Any application site reaction	13 (6.0)
Application site dermatitis	5 (2.3)
Application site pruritus	5 (2.3)
Application site dryness	4 (1.9)
Dry mouth	4 (1.9)
Application site erythema	3 (1.4)

Source: Study report, Table 12-8, p. 82

Table 38: Common Adverse Reactions (≥ 1%) by Duration of OTG Treatment in Phase 3 Study

Preferred Term	OTG < 12 weeks N=387 n (%)	OTG ≥ 12 weeks N=109 n (%)	Overall N=496 n (%)
Any adverse reactions	**69 (17.8)**	**22 (20.2)**	**91 (18.3)**
Dry mouth	27 (7.0)	3 (2.8)	30 (6.0)
Application site pruritus	10 (2.6)	3 (2.8)	13 (2.6)
Application site dermatitis	8 (2.1)	3 (2.8)	11 (2.2)
Dizziness	5 (1.3)	1 (0.9)	6 (1.2)
Headache	5 (1.3)	1 (0.9)	6 (1.2)
Pruritus (non-application site)	4 (1.0)	1 (0.9)	5 (1.0)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 18, p. 32-33

Table 39: Common Adverse Reactions (≥ 2%) in Integrated Phase 1 Studies

Preferred Term	OTG* N=215 n (%)
Any adverse reactions	**58 (27.0)**
Headache	26 (12.1)
Dry mouth	13 (6.0)
Application site pruritus	5 (2.3)
Dizziness	5 (2.3)
Nausea	6 (2.8)
Thirst	9 (4.2)
Vomiting	4 (1.9)
Pyrexia	4 (1.9)

*Inclusive of all OTG formulations, doses, and single-dose and multiple-dose studies
Source: ISS, Table 15, p. 30

SEVERE ADVERSE EVENTS:
In the double-blind phase 3 study, 16 patients in OTG group (4.1%) reported 21 severe AE's and 16 patients in placebo group (4.0%) reported 16 severe AE's. The most common severe AE's were back pain (2 OTG patients, 0 placebo patients) and headache (2 OTG patients, 0 placebo patients). Three

patients experienced severe AE's considered to be treatment-related (2 OTG patients-headaches; 1 placebo patient-sinusitis). Both of the severe headaches in the OTG group led to premature discontinuation.

During the open-label phase 3 study, 9 patients (3 on DB OTG, 6 DB placebo), or 4.2%, reported an adverse event of severe intensity. Four of these 9 patients had severe AE's considered to be treatment-related, and these AE's included application site dermatitis, application site pruritus, application site erythema, application site urticaria, and dry mouth (1 each). Two patients discontinued due to these severe application site reactions.

No subjects in the integrated phase 1 studies reported any severe adverse events.

Reviewer's comment: *The data on severe application site reactions leading to drug discontinuation should be included in the OTG label.*

ADVERSE EVENTS AND SUBGROUPS

In the phase 3 study, no significant differences in the incidence or frequency of adverse events were noted between patients older and those younger than 65 years old. 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.

Reviewer's comment: *A review of the safety dataset showed that 53% of patients ≥ 65 years (149 of 283 patients) reported any AE's compared 52% of patients < 65 years old (265 of 506 patients. Among patients ≥ 65 years, 14% experienced at least one adverse reaction, the same incidence as those < 65 years old.*

ADVERSE EVENTS IN NON-INTEGRATED STUDIES

Of the 322 subjects in the 3 non-integrated studies, 296 received at least one dose of OTG (26 partners in the person-person transference study did not directly apply OTG onto their skin). A total of 113 subjects (38%) reported 183 adverse events. The most common drug-related AE's were related to application sites. Less than 10% (7 of 113) reported an anticholinergic adverse event, such as dry mouth or blurred vision. One death unrelated to treatment occurred in the dermatoxicity study OG05004 (see "Deaths" section). No patient experienced a non-fatal serious adverse event. Eight subjects discontinued due to adverse events, 5 of which were considered treatment-related: 2 subjects due to moderate diarrhea, 1 due to mild blurred vision, 1 due to application site irritation, and 1 due to application site pruritus. The remaining 3 subjects withdrew because of unrelated urinary tract infection, alcoholism (fatality in Study OG05004), and lower back pain.

1. **Cumulative irritation study (OG05003)**: 21 of 45 subjects (47%) experienced 34 AE's. Ten of these AE's were considered to be treatment related: 8 subjects reported 8 application site pruritus, 1 subject reported application site rash, and 1 subject reported application site pain.
2. **Repeat insult sensitization study (OG05004)**: 91 of 225 subjects (40%) experienced 148 AE's. One fatal SAE unrelated to treatment occurred in a 54 year-old female subject (1039) (see "Deaths" section). Treatment-related AE's included application site pruritus (5 subjects), application site warmth (4 subjects), diarrhea (3 subjects), blurred vision (1 subject), abdominal pain (1 subject), dry mouth (1 subject), dry throat (1 subject), and non-application site pruritus (1 subject).
3. **Transference study (OG06007)**: 1 of 52 subjects experienced an adverse event (myalgia).

***Reviewer's comment**: No unexpected adverse events or adverse reactions were noted in the non-integrated studies, although these studies were of limited duration (1-21 days) and, in study OG05004, subjects were exposed only to half the to-be-marketed dose.*

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program
Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were obtained at baseline and study exit only for phase 3 study OG05009 and phase 1 study OG02020. Laboratory testing was conducted only at baseline for other integrated phase 1 studies, and no laboratory testing was conducted in the 3 non-integrated studies. The following section discusses the laboratory results only from the phase 3 study with emphasis on the findings of the double-blind period.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 *Analyses focused on measures of central tendency*
No significant differences in laboratory parameters (hematology or chemistry) were noted with respect to mean laboratory values at baseline, at endpoint, and in changes from baseline between active treatment and placebo groups. Descriptive summaries did not reveal significant differences in the mean hematology or chemistry values between patients with < 12 weeks OTG exposure and those with ≥ 12 weeks exposure.

***Reviewer's comment**: This reviewer conducted independent analyses of the laboratory dataset and concurs with the sponsor's conclusions regarding the measures of central tendency.*

7.1.7.3.2 *Analyses focused on outliers or shifts from normal to abnormal*
In the double-blind phase 3 study, the proportion of patients with shifts from normal to abnormal (high or low) did not differ significantly between placebo and active treatment groups (Table 40). In the open-label phase 3 study, the proportion of patients with shifts outside the normal range did not differ significantly between patients randomized to placebo in the double-blind period (maximum OTG exposure 12 weeks) and those randomized to OTG in the double-blind period (maximum OTG exposure 26 weeks). See Table 41.

Table 40: Patients with Shifts from Normal to Abnormal in the Double-Blind Period

Laboratory	Placebo (N=400)	OTG (N=389)
Hematocrit		
Low	13 (3.5%)	13 (3.5%)
High	4 (1.1%)	7 (1.9%)
n	372	370
Bilirubin		
Low	0	0
High	1 (0.3%)	4 (1.1%)
n	375	370
AST*		
Low	0	1 (0.3%)
High	24 (6.4%)	29 (7.9%)
n	374	369
ALT**		
Low	3 (0.8%)	2 (0.5%)
High	33 (8.8%)	36 (9.7%)
n	374	370
GGT***		
Low	1 (0.3%)	1 (0.3%)
High	21 (5.6%)	21 (5.7%)
n	375	370
Triglycerides		
Low	0	0
High	26 (6.9%)	37 (10%)
n	375	369

* AST=aspartate aminotransferase ; ** ALT=alanine aminotransferase
** GGT=gamma-glutamyl-transferase
Source: Study OG05009, 14.3.5-5, p. 3221-9

Table 41: Patients with Shifts from Normal to Abnormal in the Open-Label Period

Laboratory	DB placebo (N=107)	DB OTG (N=109)	Overall (N=216)
Bilirubin			
Low	0	0	0
High	1 (1%)	1 (1%)	2 (1%)
n	101	103	204
AST			
Low	0	0	0
High	11 (11%)	12 (11.7%)	23 (11.3%)
n	100	103	203
ALT			
Low	0	0	0
High	8 (8.0%)	11 (10.7%)	19 (9.4%)
n	100	103	203
GGT			
Low	0	0	0
High	4 (4.0%)	8 (7.8%)	12 (5.9%)
n	101	103	204
Triglycerides			
Low	0	0	0
High	8 (7.9%)	12 (11.7%)	20 (9.8%)
n	101	103	204

Source: Study OG05009, 14.3.5-5, p. 3230-8

***Reviewer's comment**: There was a relatively high proportion of patients with abnormally high AST, ALT, and triglyceride in both placebo and active groups (approximately 10%) in the double-blind period. The same trend was observed in the open-label period where approximately 10% of patients had shifts from normal to abnormal in the same LFT parameters. These observed high proportions may be systematic laboratory phenomenon, because this is trend is also observed in the placebo group.*

7.1.3.3.3 *Marked outliers and dropouts for laboratory abnormalities*

Forty-six of 789 patients (5.8%) had changes in laboratory parameters that were considered to be clinically significant and that were reported as an adverse event, although none were considered as SAE.

***Reviewer's comment:** According to the sponsor, there were no protocol-defined criteria for laboratory changes that would qualify as "clinically significant." This assessment was made at the discretion of the investigator.*

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) changes that were considered to be "clinically significant." There were 7 events of clinically significant changes in LFTs (ALT increased, AST increased, GGT increased, liver function test abnormality, hepatic enzyme increased) in the placebo group compared to 23 events in the OTG group. It was unclear how many patients had each of these 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 LFT outliers and LFT AE's are discussed below:

LFT OUTLIERS:
According to the sponsor, 10 patients (8 OTG, 2 placebo) had changes in LFT's post-randomization that met at least one of the threshold criteria (ALT, AST, or GGT values > 3X ULN or a bilirubin value > 2X ULN). The findings are summarized in the following tables.

Number of subjects meeting or exceeding specified LFT thresholds

LFT parameters	OTG N=496	Placebo N=400
ALT or AST > 3X ULN	7	2
ALT or AST > 5X ULN	3	0
Bilirubin > 2X ULN	1	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	0
GGT > 3X ULN	5	1
GGT > 5X ULN	2	0

Subjects meeting or exceeding outlier LFT thresholds

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

***Reviewer's comment**: This reviewer evaluated the LAB.xpt dataset to assess how many subjects had outlier LFT values during the double-blind period and in the overall phase 3 study. The results follow*:

Number of patient with LFT outliers during the double-blind period (Visit 7/ET)*

LFT parameters	OTG N=389 n (%)	Placebo N=400 n (%)
ALT or AST > 3X ULN	5 (1.3)	3 (0.75)
ALT or AST > 5X ULN	3	0
Bilirubin > 2X ULN	0	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	0

*Outlier values were observed at Week 7/ET

Number of patients with LFT Outliers during the phase 3 study (double-blind and open-label)*

LFT parameters	OTG N=496 n (%)	Placebo N=400 n (%)
ALT or AST > 3X ULN	8 (1.6)	3 (0.75)
ALT or AST > 5X ULN	4	0
Bilirubin > 2X ULN	1	0
Bilirubin > 2X ULN and ALT, AST > 3X ULN	0	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.

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.

This reviewer 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.

Narratives of subjects with LFT changes of special interest are discussed below. The normal ranges for the LFT parameters follow: ALP (46-118 U/L), ALT (9-29 U/L), AST (12-31 U/L), bilirubin (0.1-1.0 U/L), and GGT (6-29 U/L).

***Bilirubin > 2X ULN (1 OTG patient)**: 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 (b)(4), which decreased to (b)(4) at Visit 7 (Week 12), and increased back to a level of (b)(4) at Visit 9 (Week 26). It was unlikely that the subject's hyperbilirubinemia was drug-related. Of note, the subject did not have liver transaminase (ALT, AST), GGT, or alkaline phosphatase elevation at any time during the study.*

***ALT or AST > 5X ULN (4 OTG patients)**:*

- *Subject 10401: This was a 57 year-old white female whose baseline LFT's were slightly elevated (ALT, GGT, and ALP). She completed 12 weeks of active OTG treatment during the double-blind period. During the study, she had adverse events of poison ivy and upper molar abscess and received the following therapies: methylprednisolone, betamethasone, kenalog, dexamethasone, amoxicillin, phenoxymethylpenicillin, ciprofloxacin, lidocaine, diazepam, cyclobenzaprine HCl, pethidine HCl, and vicodin. The investigator felt that her LFT elevations*

were most likely due to her "recent intake of vicodin and antibiotics per medical history." The patient's pertinent medical history included benign liver hemagioma (1998), coronary artery disease, and cholecystecomy (1993). Concomitmant therapies at study entry were potassium chloride, aceytlsalicilic acid, glyceryl trinitrate, isosorbide dinitrate, verapramil, and atorvastatin.

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *<u>Subject 10928</u>: This was a 50 year-old white female who entered the trial with slightly elevated GGT. She completed 12 weeks of active OTG treatment in the double-blind period. Her LFT elevation at the end of treatment was considered to be "clinically significant" and an AE of "increased liver enzymes" was reported for the patient. The investigator considered the AE to be unrelated to study drug and referred the patient to her primary physician. The patient's medical history was significant for cholecystectomy (1993), hypertension (2006), and hypercholesteremia (2006). Concomitant therapies at study entry included esomeprazole, atenolol, and rosuvastatin.*

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *<u>Subject 14520</u>: This was a 51 year-old white female with a history of Hepatitis C infection (diagnosed in 1980) who entered the study with elevated LFT's (ALT, AST, GGT). She completed 12 weeks of active OTG treatment in the double-blind period; all of her LFT values further increased at the end of the double-blind period. The patient participated in the open-label portion of the study for 1 day prior to the investigator's request that her study participation*

be discontinued due to the AE of elevated liver function tests that the investigator felt to be drug-related. Follow-up LFT's obtained 21 days after her last drug dose were within normal limits (WNL).

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

- *Subject 15322: This was a 66 year-old white female with slightly elevated LFT's (ALT, GGT) at study entry. She completed 12 weeks of placebo treatment, at which time her LFT's have further increased. She completed 14 weeks of active OTG treatment during the open-label period, at which time her LFT's were further elevated. These elevations were reported as adverse events that the investigator felt were drug-related. The patient's medical history was significant for cholecystectomy (1991) and hypercholesteremia (2003). Concomitant therapies at study entry included pantoprazole, metoprolol, inegy and ibuprofen.*

A summary of her LFT's follows:

Lab/Date	(b) (4)
Visit	
ALP	
ALT	
AST	
GGT	
LDH	
Bilirubin	

n/a = not available; Scr = Screening Visit; unsc = unscheduled
Shaded cells are out-of-range; red is >3xULN

***Reviewer's assessment of LFT outliers**:*

- *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. Although ALT/AST elevations exceeding these thresholds are sensitive indicators of drug-related liver toxicity, they are relatively non-specific. There was no evidence of significant drug-related impairment of hepatic function (as indicated by no cases of drug-related clinically significant concurrent elevations in bilirubin and liver transaminase levels) in the relatively small safety database of OTG.*

- *Drug-causality could not be 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).*
- *Although the safety database of OTG is too small to exclude drug-related liver toxicity, given the extent of exposure to oxybutynin in the past 30 years and the known systemic safety profile of oxybutynin, it is unlikely that OTG has significant potential of causing severe drug-induced liver injury*.

LFT ADVERSE EVENTS:
According to the sponsor, 20 AE's related to LFT changes were reported. The following table summarizes these 20 AE's:

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	Placebo N=400		OTG N=496		Overall N=789	
Laboratory Abnormality	N (%)	Events	N (%)	Events	N (%)	Events
ALT increased	3 (0.8%)	3	5 (1.0%)	5	8 (1.0%)	8
AST increased	0 (0.0%)	0	2 (0.4%)	2	2 (0.3%)	2
GGT increased	0 (0.0%)	0	6 (1.2%)	6	6 (0.8%)	6
Liver function test abn	1 (0.3%)	1	3 (0.6%)	3	4 (0.5%)	4

***Reviewer's comment**: This reviewer conducted a review of the AE.XPT dataset and searched for all AE's related to liver function test abnormalities under MedDRA SOS of "Investigations." All of these AE's were treatment-emergent. The results follow:*

LFT AE's in Double-Blind Period (MO's analysis)

Preferred Term	OTG N=389 n (%)	Placebo N=400 n (%)
ALT increased	4 (1)	3 (0.75)
AST increased	0	0
GGT increased	4 (1)	0
LFT abnormalities	1	1
Hepatic enzyme increased	1	1
Blood bilirubin increased	0	1

LFT AE's in Double-Blind and Open-Label Periods (MO's analysis)

Preferred Term	OTG N=496 n (%)	Placebo N=400 n (%)
ALT increased	5 (1)	3 (0.75)
AST increased	1	0
GGT increased	6 (1)	0
LFT abnormalities	3	1
Hepatic enzyme increased	2	1
Blood bilirubin increased	0	1

During the double-blind period, 7 OTG patients (7/389 or 1.8%) and 6 placebo patients (6/400 or 1.5%) had at least one LFT abnormality that was considered to be an adverse event. Among the 496 patients who received at least one dose of OTG, 13 (or 2.6%) had at least one LFT abnormality considered to be an AE. The difference in the incidence of AE's related to LFT abnormality between OTG and placebo in the controlled portion of the study did not appear to be clinically significant.

PREMATURE DISCONTINUATION DUE TO LFT AE'S:

In the phase 3 study, two patients (Subjects 14505 and 14520) prematurely discontinued the open-label safety extension because of LFT elevations. Both of these patients received active OTG treatment during the double-blind period.

- Patient 14505 had a history of benign liver mass and entered the study with elevated baseline liver enzymes (ALT=(b)(4) U/L, AST (b)(4) U/L, GGT=(b)(4) U/L). The LFT's further increased after 12 weeks of OTG treatment during the double-blind period (ALT=(b)(4) U/L, AST=(b)(4) U/L, GGT=(b)(4) U/L). The patient entered open-label extension but was withdrawn 12 days later because of LFT elevations (ALT=(b)(4) U/L, AST=(b)(4) U/L, GGT=(b)(4) U/L). A follow-up evaluation 43 days following the final gel application showed ALT, AST and GGT to have decreased to levels that the investigator no longer felt to be clinically significant. The total bilirubin levels were within normal limit (WNL) at all time points.

Patient 14505: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Open-label Day 12	Follow-up (43 days after final dose)
ALT	(b) (4)			
AST				
GGT				

Normal range for ALT (9-29 U/L), AST (12-31 U/L), GGT (6-29 U/L)

- Patient 14520 had a history of hepatitis C infection and had elevated baseline ALT (b)(4) U/L), AST (b)(4) U/L) and GGT (b)(4) U/L), which also further increased after 12 weeks of OTG treatment in the double-blind period (ALT=(b)(4) U/L, AST=(b)(4) U/L, GGT=(b)(4) U/L). The patient participated in the open-label safety extension for 1 day prior to being withdrawn because of LFT elevations. At a follow-up visit 21 days after the last OTG application, the ALT and AST levels had returned to normal and GGT level had fallen below baseline levels. The total bilirubin levels were WNL at all time points.

Patient 14520: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Follow-up (21 days after final dose)
ALT	(b) (4)		
AST			
GGT			

Normal range for ALT (9-29 U/L), AST (12-31 U/L), GGT (6-29 U/L)

***Reviewer's comment**: Patients 14505 and 14520 had underlying liver disease prior to the start of the study, and the* (b) (4)

7.1.7.4 Additional analyses and explorations
No clinically relevant trends were noted for the clinical laboratory results based on geriatric status (< 65 years old versus ≥ 65 years old). The effects of gender and race on clinical laboratory parameters could not be assessed in a meaningful manner because of the limited number of male or non-Caucasian patients.

7.1.7.5 Urinalysis
Mean values, median values, and minimum and maximum for urinalysis pH and specific gravity with results expressed as percentage of Lower and Upper Normal Limit (calculated for each patient) and summary of abnormal (categorical analytes) urinalysis results at Endpoint were reviewed for differences between the 2 treatment groups. No significant findings were noted between active and placebo treatment groups at baseline and at the end of treatment.

7.1.7.6 Post-void residual
A post-void residual (PVR) urine volume was measured via ultrasound or catheter immediately after voiding at screening and at completion of double-blind phase 3 study. Overall, the mean PVR urine volume did not change across treatments and time. No significant increase in PVR urine volume was noted with OTG treatment.

Two patients with normal baseline values had PVR urine volume at end of treatment > 250 mL (one on OTG and one on placebo). An adverse event was reported for "increased post-void residual urine volume" for one patient on OTG treatment (14145) (Baseline (2/8/07) = (b) (4) mL, ET (2/26/07) = (b) (4) mL). The investigator did not consider this AE to be treatment related.

***Reviewer's comment**: Patient 14145 permanently discontinued study medication 14 days after the first dose of active OTG due to a 16-cm ovarian cystadenoma that required surgical intervention. Such a large ovarian cyst would have been present at the start of the study 14 days earlier, when the PVR volume was normal. It is unclear if this large ovarian cyst anatomically obstructed the bladder outlet leading to high PVR volume; alternatively, the high PVR volume may be secondary to an anticholinergic effect of OTG on increasing bladder storage capacity. A review of the line listing of PVR measurements for each patient on active OTG, however, did not indicate a trend of OTG use and elevated PVR urine volume.*

7.1.8 Vital Signs

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 *Analyses focused on measures of central tendencies*

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], temperature [T]): No clinically relevant trends in mean values or in mean changes from baseline to Endpoint were noted between placebo and active OTG groups, or between patients treated < 12 weeks compared to those treated ≥ 12 weeks.

***Reviewer's comment:** A review of the vital sign summaries by visit and treatment group for Study OG05009 showed no clinically significant differences in the mean or median SBP, DBP, or HR between the treatment groups.*

7.1.8.3.3 *Marked outliers and dropouts for vital sign abnormalities*
In double-blind and open-label phase 3study, analyzing for change from baseline to Endpoint vital signs, a total of 3 patients treated with OTG had vital sign values that met pre-defined criteria for "clinically

significant" changes in vital signs (1 diastolic, 2 systolic) compared to 2 patients (1 diastolic, 1 pulse) treated with placebo. In the integrated phase 1 studies, one patient in the showering study (OG06006) met the pre-defined criteria for vital sign changes (diastolic). In the non-integrated studies, no clinically significant changes were observed. No patient in the entire safety database discontinued prematurely because of vital sign changes.

Reviewer's comment: *In the phase 3 study, clinically significant changes were pre-defined as:*

- *SBP: Absolute change ≥ 20 mmHg AND endpoint SBP ≤ 90 mmHg or ≥ 180 mmHg*
- *DBP: Absolute change ≥ 15 mmHg AND endpoint DPB ≤ 50 mmHg or ≥ 105 mmHg*
- *HR: Absolute change ≥ 15 beats per minute (bpm) AND endpoint pulse ≤ 50 or ≥ 120 bpm.*

In the 74-Day letter, the Division requested the sponsor to analyze clinically significant changes in vital signs for the absolute change from baseline separately from those exceeding a pre-defined value for each clinic visit. The sponsor submitted these analyses to the NDA in Amendment 0004 dated to August 27, 2008. A detailed review of these analyses did not reveal any vital sign trends of safety concern. Overall, the incidence of vital sign outliers was similar between placebo and active groups and between patients treated with < 12 weeks and those treated ≥ 12 weeks across clinic visits.

7.1.9 Electrocardiograms (ECGs)

No specific QT study was performed. Safety ECG's were obtained at baseline and exit only during the double-blind phase 3 study. No trends toward change in ECG were noted in the phase 3 study. Overall, slightly higher proportion of placebo than OTG patients had ECG's that "worsened" from baseline (10% in OTG versus 13.1% in placebo). Nine ECG's (5 on OTG, 4 on placebo) were considered to be clinically significant.

Reviewer's comment: *A review of the ECG dataset (AF-ECG.XPT) was conducted to evaluate all study exit ECG's considered as "abnormal, clinically significant." In all, 8 placebo and 7 OTG patients had such ECG reading at study exit. Of these patients, 3 placebo and 4 OTG patients had "abnormal, clinically non-significant" baseline ECG's; 2 placebo patients and 1 OTG patient had "normal" baseline ECG. The incidence of clinically significant ECG changes in the OTG group was similar to placebo.*

7.1.12 Special Safety Studies

7.1.12.1 Skin tolerability

Local skin tolerability was assessed in the integrated 11 studies by visual inspection of the application area at variable time intervals post-application. Skin tolerability was graded based on the following erythema scale:

Erythema Scoring Scale

Score	Rating	Erythema at application site
0	None	None
1	Mild	Faint/barely perceptible
2	Moderate	Bright pink or sunburned appearance
3	Severe	Beet red appearance

Double-blind phase 3 study: Application sites were evaluated for erythema changes at each clinic visit; 1466 and 1495 application sites were evaluated in the OTG and placebo groups, respectively. The results across all visits in DB period are summarized in Table 42.

Table 42: Erythema Assessment in Double-Blind Phase 3 Study

Erythema Assessment (# of evaluations)	OTG (1466)	Placebo (1495)
Mild	14 (1.0%)	13 (0.9%)
Moderate	5 (0.3%)	0
Severe	0	0

Source: Summary of Safety, Module 2.7.4, Table 2.7.4-18, p. 29

Duration of active OTG treatment: 1634 application sites were evaluated in patient with < 12 weeks OTG treatment and 620 application sites in patients with ≥ 12 weeks of treatment. The findings across all visits by duration of treatment group are summarized in Table 43.

Table 43: Erythema Assessment in Phase 3 Study by Duration of OTG Therapy

Erythema assessment (# of evaluations)	< 12 weeks (1634)	≥ 12 weeks (620)	Overall (2254)
Mild	15 (0.9%)	6 (1.0%)	21 (0.9%)
Moderate	4 (0.2%)	2 (0.3%)	6 (0.3%)
Severe	0	0	0

Source: Summary of Safety, Module 2.7.4, Table 2.7.4-19, p. 29

Integrated Phase 1 studies: Table 44 summarizes the findings of application site erythema assessments in the 10 integrated phase 1 studies in healthy volunteers. Erythema assessments were conducted 1 and 24 hours post-application.

Table 44: Erythema Assessment in the Integrated Phase 1 Studies

Erythema evaluation	All OTG Erythema events/ # of evaluations (%)	Oxytrol TDS Erythema events/ # of evaluations (%)
Mild		
1 hr	0/372	8/41 (20)
24 hr	1/565 (0.2)	4/41 (9.8)
Moderate		
1 hr	0	0
24 hr	0	1/41 (2.4)
Severe		
1 hr	0	1/41 (2.4)
24 hr	0	0

Source: Clinical Summary, Module 2.7.4, Table 2.7.4-17

Reviewer's comment:

- *There were no cases of severe erythema in the protocol-defined assessments. However, one patient who discontinued prematurely because of an application site reaction had severe erythema (11815). The incidence of any erythema was minimal (≤ 1%).*
- *Erythema changes did not appear to worsen significantly with longer duration of drug exposure.*

Reviewer's comment: *Although OTG treatment had minimal erythema changes, the sponsor's erythema scoring system is a limited assessment of local skin tolerability. Local skin reactions, such as edema, induration, and other changes are not captured by this scoring system. The results of the erythema*

evaluation should be combined with the application site adverse reaction data to better assess skin tolerability of OTG.

- *During the double-blind phase 3 study, 21 or 5.4% OTG patients versus 4 or 1% placebo patients reported at least one application site reaction. Less than half of these OTG patients (8 of 21) had any erythema changes. During the open-label phase 3 study, 6% of patients reported at least one application site reaction.*
- *Among patients who received at least one dose of active OTG (either in the double-blind or open-label period or both), 6.7% reported at least one application site reaction.*
- *In the double-blind and open-label phase 3 study, 2.4% of OTG-exposed patients (compared to 0.8% of placebo) discontinued prematurely because of an application site reaction. A majority of patients who discontinued because of an application site reaction did not have erythema changes.*
- *Compared to patients treated with OTG < 12 weeks, more patients who received OTG ≥ 12 weeks reported at least one application site reaction (8.3% versus 6.2%) and more discontinued because of an application site reaction (3.7% versus 2.1%).*
- *Common application site reactions were pruritus (most common), dermatitis (second most common), erythema, and papules.*

Although there are no clinical trials directly comparing the skin tolerability of the 2 transdermal oxybutynin products, controlled clinical trial data indicate that the skin tolerability of OTG appears to be better than Oxytrol. According to a clinical review of the Oxytrol NDA (NDA 21-351/S000), of the 3173 application sites evaluated in OAB patients treated with Oxytrol, 36% showed mild erythema, 14% showed moderate, and 0.8% showed severe erythema compared to ≤ 1% with OTG in Study OG05009. In the phase 3 clinical trials of Oxytrol, approximately 23% of patients on active treatment reported at least one application site reaction compared to 6.7% of OTG-exposed patients in OG05009. In the Oxytrol trials, 7-9% of patients treated with active Oxytrol discontinued prematurely because of an application site reaction compared to 2.4% of OTG-exposed patients in OG05009

7.1.12.2 Dermatoxicity

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. The objective was to evaluate the incidence and severity of cumulative skin irritation. 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.

Reviewer's comment: *The sponsor evaluated the potential cumulative irritant effect of placebo and active (1 g 10% OTG) gels in New Zealand White rabbits (ONY00012). Under the test conditions, both placebo and active gels were considered to be non-irritants.*

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 10%. 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-minute, 24-hour, 48-hour, and 72-hour after gauze removal.

***Reviewer's comment**: Skin hypersensitivity to OTG 10% should be adequately labeled in the Warnings and Precaution section of the label. Patients who experience skin hypersensitivity to OTG should discontinue treatment. Furthermore, because patients with drug-related skin hypersensitivity may rarely experience systemic hypersensitivity when re-challenged with the active drug, caution should be used when starting these patients on other oxybutynin products.*

Because the dose-dependence for skin sensitization with OTG is unknown, it is unclear if the incidence of skin hypersensitivity using 0.5 g of OTG would be the same as the 1 g dose. To err on the conservative side, this reviewer considers the skin hypersensitivity incidence of 0.5% observed in Study OG05004 to be a low estimate for 1 g 10% OTG.

The dermal sensitization potential of placebo and active gels was evaluated in Hartley-derived albino guinea pigs (ONY00013). Under the test conditions, both active and placebo gels were not considered to be contact sensitizers.

7.1.12.3 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 from 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 Cmax = 0.94 ng/mL, mean AUC [0-48 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 Cmax =0.02 ng/mL) starting at 8 hours post-dose and which were still detectable at 48 hours post-dose.

***Reviewer's comment**: 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 can be adequately addressed in the product label.*

7.1.14 Human Reproduction and Pregnancy Data

Two pregnancies occurred during the clinical trials with OTG. In Study OG05003 (21-day cumulative skin irritation study), Subject 844 had a positive urine pregnancy test on (b) (6), following (b) (6) consecutive daily applications of 1 g OTG 10%. The subject carried the pregnancy to term and delivered a healthy, full-term baby on (b) (6). No maternal or fetal complications were reported. In Study OG06005 (comparative steady state PK of 1 g 10% OTG and Oxytrol TDS), Subject 1308 had a positive urine pregnancy test on (b) (6), following (b) (6) days of treatment with Oxytrol oxybutynin transdermal system (3.9 mg/day) and 11 days of daily treatment with 1 g 10% OTG. The subject was lost to follow-up. According to the sponsor, a third party reported that the subject carried the pregnancy to term and delivered a healthy baby on (b) (6).

Oxybutynin is a Pregnancy Class B based on preclinical data showing no evidence of impaired fertility or harm to the animal fetus. There are no human pregnancy data with oxybutynin.

7.1.16 Overdose Experience

According to oxybutynin product labels, overdosage with oxybutynin has been associated with anticholinergic effects, such as central nervous system excitation, dehydration, cardiac arrhythmia, and urinary retention.

Although no clinical overdose experience exists with OTG, plasma concentrations of oxybutynin decline starting at 24 hours after gel application. Patients should be monitored accordingly.

7.2.9 Additional Submissions, Including Safety Updates

The following additional sources were reviewed for safety information related to transdermal oxybutynin:

- *120-Day Safety Update*: This safety update covers the period of January 1, 2008, to July 15, 2008. The sponsor had no additional clinical safety update to report during this safety update time period.
- *Annual report for IND 67,126* (OTG for the treatment of OAB): This annual report covers the period from April 1, 2007, to March 31, 2008. No new or unexpected safety information was noted.
- *Periodic Adverse Drug Experience (ADE) Annual Report for NDA 21-351 (Oxytrol TDS 3.9 mg/day) supplemented with this reviewer's AERS database reports*: This annual report covers the period from February 26, 2007, through February 25, 2008. There were 2 notable ADE reports:

    1. 15-Day Safety report (MedWatch report #5390808): a 67 year-old female started treatment with Oxytrol TDS for U-UI on June 17, 2007. (b) (6) days later, she experienced "global transient amnesia" for 6 hours associated with a fall. Her diagnostic workup (brain CT, EKG, carotid Doppler, EEG) was normal. She has no significant medical history and concomitant medications included estrogen cream (Premarin), zopiclone (Imovane), and mometasone furoate nasal spray (Nasonex). The patient was treated and discharged from the emergency room. The patient discontinued treatment with Oxytrol, although no other follow-up information was available.
    2. 15-Day Safety report (MedWatch report #5606632): a 60 year-old female experienced "aphasia, slow speech, and showed signs of anticholinergic overdose after applying her first Oxytrol patch" on (b) (6). Her husband reported that she woke up from her sleep and was found on the floor "confused, drowsiness/somnolence, dry mouth, and inability to talk/word finding difficulties." The patient may have fallen but did not lose

consciousness. Her diagnostic workup in the emergency room was normal (vitals, laboratory tests, EKG, CT of the head, chest X-ray, cardiac enzymes). She was admitted for observation overnight, treated symptomatically, and discharged the following day with resolution of her symptoms. She discontinued Oxytrol treatment while in the emergency room. The patient has no significant medical history and the report indicated that "her routine home medications were continued," although concomitant medications were not listed. The report also indicated a diagnosis of "possible drug reaction with Oxytrol."

Reviewer's comment: *Drug-causality cannot be ruled out in both of the above cases. However, given that there were only 2 cases of notable neurological impairment (out of estimated 390,000 new prescriptions in the U.S. during the reporting period), this reviewer does not believe this reporting frequency rises to the level of safety labeling for all transdermal oxybutynin products.*

A review of other periodic ADE reports indicate that there were 1 serious AE of "visual hallucination," and one report of "hallucination," 2 cases of "confusional state," and 6 cases of "balance disorder." Many of these AE's occurred in the setting of other concomitant medical conditions (e.g., Parkinson's disease, stroke, dizziness), although the psychiatric and neurologic adverse effects of antimuscarinic therapy, especially oral oxybutynin, is known. This reviewer does not believe these reporting frequencies rise to the level of safety labeling for all transdermal oxybutynin products.

- *Annual Report for NDA 21-351 (Oxytrol TDS 3.9 mg/day):* No new safety findings were noted.

7.3 SAFETY CONCLUSIONS

- The safety profile of OTG 10% is overall acceptable with the expected anticholinergic systemic effects of a transdermal oxybutynin product. Although no studies directly comparing the 2 transdermal products exist, the skin tolerability of OTG 10% appears to be better than that of the oxybutynin transdermal system (Oxytrol TDS).
- Contact hypersensitivity to OTG reactions occurs at an incidence of 0.5%.
- 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.

8 ADDITIONAL CLINICAL ISSUES

8.1 DOSING REGIMEN AND ADMINISTRATION

The to-be-marketed dose and dose regimen is a fixed regimen of 1 g 10% OTG applied once a day. This dose was based on PK similarity with Oxytrol TDS. No other doses or dose regimens were evaluated for clinical safety and efficacy in the clinical development of OTG.

8.2 DRUG-DRUG INTERACTIONS

No drug-drug interaction (DDI) studies were conducted with OTG. This reviewer does not consider any specific DDI study with OTG to be necessary at this time.

8.3 SPECIAL POPULATIONS

Geriatrics: In the phase 3 study, approximately 35% of patients were at least 65 years old. No clinically differences in safety or efficacy were noted between these patients and younger patients. This reviewer does not consider dose adjustment in patients ≥ 65 years old to be necessary.

Pediatrics: OTG has not been evaluated in individuals younger than 18 years of age. In the original NDA submission dated March 26, 2008, the sponsor requested a waiver of pediatric studies in children under the age of five and a deferral of pediatric studies in children ages 5 to 17 years until after the approval of OTG for use in the adult population.

In Amendment 0005 dated September 11, 2008, submitted to the NDA, sponsor submitted a proposed Pediatric Protocol Synopsis for the deferred pediatric population. The Pediatric Plan relies extensively on the findings of Study OGO03010, which the sponsor conducted in response to a BPCA Written Request for Oxytrol TDS dated May 14, 2004. The sponsor proposed an open-label, uncontrolled, PK and safety study in 40 children ages 5-15 years with detrusor overactivity associated with a neurological condition to bridge to the findings of Study OG03010. In a letter dated November 18, 2008, the Division informed the sponsor that a clinical safety and efficacy trial in the deferred pediatric population would be necessary. In Amendment 008 dated December 5, 2008, the sponsor proposed a trial evaluating the safety and efficacy of OTG in children ages 5-15 with urinary frequency and daytime incontinence NOT due to a neurologic condition. The Division informed the sponsor in a teleconference on December 18, 2008, that a pediatric population where the potential benefits of an anticholinergic therapy may outweigh the risks is children with neurogenic bladder. The Division advised the sponsor to submit a pediatric plan outlining a dose-finding PK/PD study in the deferred pediatric population and a clinical safety and efficacy study in the same population. In response, the sponsor submitted a revised pediatric plan for the deferred population outlining a PK/PD dose-finding study in approximately 30 children with neurogenic bladder followed by a safety and efficacy study in 60 children with neurogenic bladder. The final study reports of these 2 studies would be submitted to the FDA by September, 2012 (PK/PD study) and August, 2015 (safety and efficacy study). Although the Division did not agree to any specific details of the study synopses and this was conveyed to the sponsor during the labeling negotiation teleconference on January 13, 2009, the revised pediatric plan was sufficient for the Division to recommend a deferral of the pediatric studies in children ages 6 to 16 years, 11 months. PeRC concurred with the Division's recommendation.

Gender/Race: The number of patients in the phase 3 study who were male or non-Caucasian was too limited to draw any meaningful conclusions about the effect of gender or race on the safety or efficacy of OTG.

Hepatic or Renal Impairment: The pharmacokinetics of OTG was not evaluated in patients with renal impairment or liver insufficiency.

9 OVERALL ASSESSMENT

9.1 CONCLUSIONS

In summary, the treatment benefits outweigh the risks for 1 g 10% OTG once daily in adults with symptomatic overactive bladder not related to pathological or metabolic disorders or medication use. Study OG05009 demonstrated that OTG treatment resulted in statistically significant improvement in the primary endpoint (number of daily urinary incontinence episodes) and the key secondary endpoint (urinary frequency) compared to placebo after 12 weeks of treatment. The improvement in these clinical

endpoints was clinically meaningful. The safety and tolerability profile of 10% OTG was generally consistent with the known adverse event profile of the oxybutynin transdermal system (Oxytrol TDS) and other oxybutynin products. The skin tolerability of 10% OTG, however, appeared to be better than that of the oxybutynin transdermal system (Oxytrol TDS). Two main safety issues with OTG were the definite potential for dermal transfer of oxybutynin with direct skin-to-skin contact at the application site and skin sensitization. Both of these issues, however, can be adequately addressed in the product label.

9.2 RECOMMENDATION ON REGULATORY ACTION

From a clinical perspective, this reviewer recommends the approval of this NDA pending the Office of Compliance's recommendation regarding the acceptability of the manufacturing sites.

9.3 RECOMMENDATION ON POSTMARKETING ACTION

This reviewer recommends routine post-marketing surveillance. All suspected skin sensitization reactions should be reported as 15-Day Reports.

9.4 LABELING REVIEW

The following major clinical labeling changes are recommended and have been made othte proposed label:

1. Highlights of Prescribing Information:

a. Indications and Usage: The word "antispasmodic" in the description of the pharmacologic class of OTG is not a well-recognized pharmacologic class and should be deleted.

b. Warnings and Precautions:
   - Safety information on the risk of skin sensitization, potential for skin transference with OTG, and flammable alcohol-based gel should be included.

2. Full Prescribing Information

a. Contraindications (Section 4): OTG should be contraindicated in patients who experience hypersensitivity, including skin sensitization, to the product.
b. Warnings and Precautions (Section 5): This section should include safety information on skin sensitization and skin transference.
c. Adverse Reactions (Section 6): This section should contain general clinical summary of the adverse reaction profile and adverse reactions which led to study withdrawal. Table 1 should reflect common AE's where the incidence in the OTG group is > 2% and > placebo to present the AE data in balanced manner without judgment as to drug-causality. The safety data on application site reactions should also be presented.
d. Clinical Studies (Section 14):
   i. The results of the Incontinence Impact Questionnaire (IIQ) and King's Health Questionnaire should not be included in the product label. Both of these endpoints, which are not included in any other OAB product labels, are considered exploratory, and have not been adequately validated for labeling claims.

10 APPENDICES

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS

10.1.1 Appendices of Study OG05009

a. Schedule of Events for Screening, Double-Blind, and Open-Label Periods

Assessments	Screening/Baseline Period				Double-Blind Treatment				Open-Label Treatment	
	Initial Evaluation	Wash-out	Start of Baseline	End of Baseline						
Patient Visits	V_1	2-week Washout/Training Period	V_2	V_3	V_4	V_5	V_6	V_7/ ET	V_8	V_9/ET
Weeks	-3		-1	0	1	4	8	12	19	26
Informed Consent	X							X		
Medical History	X									
Physical Examination			X					X		
Concomitant Medications	X		X	X	X	X	X	X	X	X
Vital Signs	X		X	X	X	X	X	X	X	X
Urinalysis			X					X		X
ECG			X or	X				X		
Serum Chemistries[1]			X					X		X
CBC			X					X		X
PSA (Males only)			X							
Urine beta-HCG[2]				X				X		X
3-Day Urinary Diary[3]				X	X	X	X	X		
2-Day Voided Volume[4]				X	X	X	X	X		
PVR				X				X		
QoL Questionnaires				X	X	X	X	X		X
Plasma Concentration					X	X	X	X		
Study Drug Dispensed				X		X	X	X[5]	X[5]	
Daily Gel Application					X	X	X	X	X	
Skin Tolerability Assessment					X	X	X	X	X	X
AE Assessment					X	X	X	X	X	X

[1] Fasting

[2] Urine beta-HCG tests was only performed for female patients of child-bearing potential

[3] A 3-day (consecutive days) urinary diary was recorded during the week immediately prior to the indicated visit beginning at least 4 days prior to the visit.

[4] During two consecutive days of the 3-day diary, patients were required to collect all urine during normal voids and record the voided volume on the diary card.

[5] Patients in open-label extension only

Source: Study report, Table 9-3, p. 27

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b. Eligibility Criteria

Inclusion:

1. Male or a non-pregnant, non-lactating female using adequate means of birth control, if not menopausal
2. At least 18 years of age
3. History of overactive bladder with symptoms of urgency, urge urinary incontinence, and urinary frequency, with or without neurological disease
4. Recorded an average of ≥ 8 urinary voids per day and ≥ 4 urge urinary incontinence episodes during the 3-day baseline diary period
5. Average recorded urine void volume of ≤ 350 mL per void during the 2-day urine collection of the 3-day baseline urinary diary
6. History of pure urge or mixed urinary incontinence with a predominance of urge incontinence episodes (on baseline diary)
7. Post-void residual urine volume of ≤ 250 mL, as measured by ultrasound or catheterization
8. Capable of completing the urinary diary without assistance

Exclusion: Patients were excluded from participation based on the criteria outlined in the protocol. These criteria were established primarily to exclude patients whose incontinence may have been related to chronic illness, anatomical weakness/abnormalities or concomitant medications.

1. Did not complete all 3 days of the 3-day urinary diary during the baseline assessment
2. History of lower urinary tract surgery within the past six months
3. Continuous small volume urine loss/leakage
4. Clinically significant systemic disease or condition that would, in the investigator's opinion, lead to undue risk following administration of oxybutynin
5. Laboratory value(s) outside the normal range that were, in the opinion of the investigator, clinically significant and could interfere with the patient's participation or outcome/interpretation of the study
6. History of alcohol/drug abuse within the past year
7. Known hypersensitivity to oxybutynin or related compounds, or any component of the gel formulation
8. Active skin disorder, such as eczema, seborrhea, or psoriasis affecting the gel application areas
9. Known uncontrolled narrow angle glaucoma
10. One or more treatable conditions that may cause urinary incontinence or urgency (e.g., urinary tract infection, prostatitis, hematuria, urinary tract obstruction, urethral diverticulum, bladder tumor, bladder stone, prostate cancer, fecal impaction, requirement for acute or intermittent use of diuretics, excessive use of alcohol) [Note: Patients with acute urinary tract infection may have been treated for infection and then re-evaluated for entry into the study.]
11. Diagnosis of interstitial cystitis, urethral syndrome, or painful bladder syndrome
12. Gastrointestinal conditions such as partial or complete obstruction, pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic), decreased gastrointestinal motility (paralytic ileus, intestinal atony, chronic and severe constipation), or risk of gastric retention
13. Male patient with a PSA > 4 ng/mL. Patients with PSA ≤10 ng/mL and negative prostate biopsies within 1 year prior to study entry were acceptable (Note: Patients who had undergone a prostate biopsy within the previous 3 months were not eligible)
14. History of prostate biopsy positive for prostate carcinoma
15. History of significant medical problems that could have confound the outcome of the study (e.g., > 3 urinary tract infections within the past 12 months, unstable diabetes mellitus, anticipated changes in hormonal status [patients receiving hormone treatments were requested to maintain the same hormone treatment regimen throughout the study period])

16. Diagnosis of overflow incontinence secondary to under active or acontractile detrusor or outlet obstruction, or other evidence of significant outlet obstruction (including benign prostate hyperplasia)
17. Required concomitant medications that may affect detrusor activity, including tricyclic antidepressants (e.g., imipramine, doxepin, desipramine, and nortriptyline)
18. Excessive consumption of caffeine (> 5 cups of coffee, tea, or cola daily)
19. Could not maintain usual program of nonpharmacologic management of incontinence (e.g., pelvic floor exercise and timed voiding/bladder training) during the study
20. Participated in another investigational drug study within 30 days prior to the first study drug administration
21. Judged by the investigator to be unsuitable for enrollment in this study for any reason

10.1.2 Study OG05003

Study Title: "A 21-day cumulative irritation study of topically applied oxybutynin gel and placebo gel in healthy volunteers"

Study period: October 2005-November 2005

Objective: To calculate the incidence and evaluate the degree of cumulative skin irritation associated with repetitive 24-hour applications of active and placebo Oxybutynin Topical Gel to the same sites during a 21-day study period

Study design and conduct: This study was a single-center, evaluator-blinded, multiple-application study. Subjects received applications of the two gels daily (1 g OTG 10% gel and matching 1 g placebo gel), applied to the same application sites on the back and then covered with a 4 x 4 inch gauze pad for 24 ± 2 hours over the 21-day period. A left and right application site on the back was randomized for treatment with active or placebo gel for each subject for the duration of the study. Subjects reported to the clinic for daily gel application and dermatologic evaluations on an outpatient basis. Dermatologic evaluations were performed prior to the first system application, at the time of removal of each gauze pad, and approximately 24 hours following the final pad removal. The dermal evaluators were blinded to the application sites of the test and control systems. Safety evaluation consisted of monitoring adverse events.

Reviewer's comment: *The Cumulative Skin Irritation Study design usually calls for occluded applications to detect irritation under maximum stress conditions. Study OG05003 investigates the cumulative irritation potential of OTG 10% under modified conditions of maximal stress. Rather than using the occlusive patch, the study used an open patch method to better simulate conditions of therapeutic use. The Division previously agreed that such modification was acceptable for a topical gel.*

Otherwise, the remainder of the general study design and conduct of OG05003 are consistent with the Agency's recommendations for a Cumulative Skin Irritation Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).

Summary of study schedule:

PROCEDURE	SCREEN	DAY 1	DAY 2 to 21	DAY 22	DAY 23
Informed Consent	X				
Urine Pregnancy Eval.[1]	X	X			X
Medical/Drug History	X				
Physical Examination	X				
Gel Applications		X	X		
Dermatologic Evaluation[2, 3]		X	X	X	X
Concomitant Medication Use		X	X	X	X
Adverse Event Monitoring		X	X	X	X

[1] *For female subjects of child-bearing potential at screen, prior to first dose and at exit from study*
[2] *Before initial application and following removal of each gauze pad and 24 hours post removal of final pads*
[3] *Photographs will be taken only if grade 3 skin reaction is present.*

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Eligibility criteria:
Inclusion:

- Male or female, 18 to 65 years old
- Provide written informed consent
- Willing to use an acceptable method of birth control during study participation

Exclusion:

- Pregnant or nursing (females only)
- Contraindications to oxybutynin therapy or intolerance of other anticholinergic medications
- Hair, tattoos, pigmentation, scars, moles or other conditions at the area of gel applications that may interfere with applications, tolerability, or post-application evaluation
- Clinically significant skin condition at application sites that contraindicates participation, including psoriasis, eczema, atopic dermatitis, and active cancer within one year
- Participation in a Draize-type patch test or cumulative irritation test within the past 4 weeks
- Participation in a primary irritation test or soap chamber test within the past 4 weeks
- Participation in a clinical trial or receipt of an investigational medication within 1 month of the study
- Routine use of anti-inflammatory, immunosuppressive or antihistamine medications (81 mg of aspirin daily for cardiovascular prophylaxis was allowed)
- Allergy injections
- Health history including any one or combination of these diagnosis: severe asthma, active immunologic disorders, insulin dependent diabetes, glaucoma
- Clinically significant chronic illness which could place the subject at increased risk during participation or result in inappropriate dermal response during the study
- History of alcohol or drug abuse within 1 year of the study
- Inability to provide written informed consent
- Judged by the investigator to be unsuitable for any reason

Evaluation variables:
The skin potential of the gel systems was evaluated in terms of cumulative irritation. The cumulative irritation score was determined for each subject using the following score system by Berger and Bowman described in Table 1. A numeric score was assigned when a clinically significant skin response was noted or ≥ 25% of the test site area showed a skin response.

Table 1: Scoring Scale of Berger and Bowman

Skin response	
Dermal reactions	**Numeric score**
No evidence of irritation	0
Minimal erythema, barely perceptible	1
Definite erythema, readily visible or minimal edema or minimal papules	2
Erythema and papules	3
Definite erythema	4
Erythema, edema, and papules	5
Vesicular eruption	6
Strong reaction spreading beyond test site	7
Response of superficial layers of the skin	
Surface skin reactions	**Letter score (equivalent numeric score)**
Slight glazed appearance	A (0)
Marked glazing	B (1)
Glazing with peeling and cracking	C (2)
Glazing with fissures	F (3)
Film of dried serous exudate covering all or portion of the test site	G (3)
Small petechial erosions and/or scabs	H (3)

***Reviewer's comment**: The above scoring system was one example of an acceptable scoring system to quantify skin reactions in a Cumulative Skin Irritation Study or a Skin Sensitization Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).*

Statistical consideration:

Sample size: A sufficient number of healthy subjects were enrolled to ensure that 30 subjects complete the study. This is a standard sample size for a 21-day cumulative irritation study.

Analysis population: The cumulative irritation evaluation analysis will be based on the Evaluable population, which consisted of all subjects who completed the study and those withdrawn due to skin reaction score of ≥ 3. The Evaluable population did not include subjects who discontinued prematurely for other reasons. Safety analysis will be based on the Safety population, which included all subjects who received at least one dose of study drug.

Cumulative irritation analysis: The actual test score consisted of a combination of the numeric and letter grades (described by the Berger and Bowman scoring system). Letter grades were converted into numerical equivalents: A=0; B=1; C=3; and F, G, and H = 3. These numeric equivalents are additive to a

numerical score. The cumulative irritation score was determined for each subject by treatment. An individual score of 3 will be carried forward for any discontinued subject for the remaining evaluation time points. Descriptive statistics on individual scores were provided by treatment and application day. The total cumulative irritation score was summarized using descriptive statistics. For the calculation of total score, an upper limit of 3 was selected for reaction scores > 3. According to the sponsor, it would be meaningless to use a score > 3 (extreme irritation) because the "intent of this test is to compare treatments that are relatively mild." The total cumulative irritation score was normalized to a base of 10 average. The irritation of test and control systems was classified according to an empirically derived categorization system described below:

Classification system of interpretation of Base 10 Irritation Scores

Score	Class	Indications from Test	Description of Observed Responses
1	0-49	Mild article - no experimental irritation	Essentially no evidence of cumulative irritation under conditions of test (i.e., continuous reapplication and occlusion at concentration specified).
2	50-199	Probably mild in normal use	Evidence of a slight potential for very mild cumulative irritation under conditions of test.
3	200-449	Possibly mild in normal use	Evidence of a moderate potential for mild cumulative irritation under conditions of test.
4	450-580	Experimental cumulative irritant	Evidence of a strong potential for mild to moderate cumulative irritation under conditions of test.

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This classification system is designed to differentiate the irritation potential of relatively mild test materials.

***Reviewer's comment**: The sponsor used the same cumulative irritation analysis and classification system of interpretation for the irritation potential with the oxybutynin transdermal system (Oxytrol TDS). According the medical officer's review of the Oxytrol NDA, active transdermal system produced a Class 4 irritation score and placebo transdermal system produced a Class 3 score.*

Subject Disposition:
A total of 45 subjects (14 males, 31 females) were enrolled and 41 subjects completed the study. One subject withdrew due to unrelated adverse event (lower back pain) and 3 other subjects withdrew due to personal reasons (schedule conflict).

Demographics and baseline characteristics:
Subjects were primarily non-Hispanic (93%) White (100%) men (30%) and women (70%) with an average (SD) age of 36 (12) years.

Cumulative Irritation Analysis:
The Evaluable population consisted for 41 subjects. 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.

***Reviewer's comment**: A review of the skin assessment actual visual scores at each visit (table 14.2, p. 37 of study report) was conducted. One subject (subject #8) had severe irritation (score of 7) after the 3rd dose on both the placebo and active gel sites. This patient was withdrawn from the study and a converted*

score of 3 was carried forward in the cumulative irritation analysis. No other subject had an actual irritation score ≥ 3 at any skin evaluation. Six subjects (2, 3, 11, 27, 30, 43, or 13%, had a skin evaluation with a score of 2 at the OTG site; 2 subjects (26, 32), or 4%, had a skin evaluation with a score of 2 at the placebo site.

Safety analysis:

- *Extent of exposure*: Forty subjects received all 21 applications. One subject received 2 doses prior to scoring an irritation score of 7 and was withdrawn. Four other subjects received 1-13 applications prior to discontinuing the study for reasons unrelated to treatment.

- *Adverse events*: No deaths or non-fatal serious adverse events occurred. A total of 21 subjects (47%) reported 34 adverse events. Ten of the 34 adverse events were considered treatment-related with the most common adverse reaction being application site pruritus (8 events in 8 subjects). There were no severe AE's.

- Pregnancy: One subject (844) had a positive urine pregnancy test at study exit. The outcome of the pregnancy was unremarkable.

Reviewer's assessment: Under test conditions of near maximal stress, OTG has no evidence of cumulative irritation.

10.1.3 Study OG05004

Study Title: "A repeat insult sensitization test of active and placebo topically applied oxybutynin gel in healthy volunteers"

Study period: January 2006 - March 2006

Objective: To evaluate the incidence of contact sensitization following repetitive applications of active and placebo oxybutynin gel

Study design and conduct: This was a single-center, single-blind, repeat insult patch test of active and placebo oxybutynin gel. Each subject received both test materials (0.5 g OTG 10% and 0.5 g placebo gel) applied to contralateral shoulders and covered with a gauze pad. The assignment of the test gels was randomized within each subject. The test materials were applied 3 times a week for 3 consecutive weeks (induction phase). A trained skin evaluator blinded to the application sites of the test and control systems conducted skin evaluations within 5 minutes of gauze removal and prior to the next gel application. After the induction phase, a rest period of 2 weeks was followed by a single 48-hour challenge application with skin evaluations at 5 minutes, 24 hours, 48 hours, and 72 hours after gauze removal. Safety evaluations consisted of monitoring of adverse events.

Reviewer's comment: Reviewer's comment*: According to the sponsor, the study design was the "Jordan-King modification of the Draize Procedure that is the standard study design for human repeated insult patch test." The study investigates the sensitization potential of OTG 10% under modified conditions of maximal stress. Rather than using the occlusive patch, the study used an open patch method to better simulate conditions of therapeutic use. This modification is acceptable. Otherwise, the remainder of the study design and conduct of OG05004 are consistent with the Agency's recommendations for a Skin*

Sensitization Study published in the now-withdrawn draft Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products (December, 1999).

Summary of study schedule:
Induction Period:

Visit	INDUCTION PERIOD											
	1		2	3	4	5	6	7	8	9	10	Make up[1]
Study Day	Up to -28	1	3	5	8	10	12	15	17	19	22	24
Obtain Consent	X[2]											
Inc/Exc Criteria	X[2]											
Medical History	X[2]											
Vital Signs and Skin Evaluation		X										
Pregnancy Test (women of childbearing potential)		X										
Test Article Application		X	X	X	X	X	X	X	X	X	X[1]	
Pad Removal			X	X	X	X	X	X	X	X	X	X[1]
Skin Reaction Evaluation			X	X	X	X	X	X	X	X	X	X[1]
Assess AE's		X	X	X	X	X	X	X	X	X	X	X[1]
Deviation Documentation		X	X	X	X	X	X	X	X	X	X	X[1]
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X[1]

[1] Procedures or visit only required for subjects missing one visit.
[2] Procedures may have been conducted on day 1.

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Challenge Phase:

Visit	REST PHASE	CHALLENGE PHASE				
	none	11	12	13	14	15
Study Day	22-35	36	38	39	40	41
Pregnancy Test (women of childbearing potential)		X				X
Test Article Application		X				
Pad Removal			X			
Skin Reaction Evaluation			X	X	X	X
Assess AE's		X[1]	X	X	X	X
Deviation Documentation		X	X	X	X	X
Concomitant Medication		X[1]	X	X	X	X
Termination Sheet						X[2]

[1] Adverse events experienced and use of concomitant medication during the rest phase were recorded.
[2] Completed at the final visit or at any time the subject was prematurely discontinued.

<u>Eligibility Criteria</u>:
Inclusion:

- Male or female, 18 to 65 years old
- Using effective contraception or of non-childbearing potential (women only)
- Non-pregnant (negative pregnancy test on Day 1)
- Healthy
- Provide informed consent

Exclusion:

- Pregnant or lactating
- Known or suspected hypersensitivities to oxybutynin or other anticholinergic agents or any component of the gel formulation
- History of narrow angle glaucoma, urinary or gastric retention, or significant sensitivity or allergy to adhesive bandages, tapes, etc.
- Hair, tattoos, pigmentation, scars, moles or other conditions to the area to be treated that may interfere with the application, tolerability, or post-application evaluations
- Clinically significant skin conditions (psoriasis, eczema, atopic dermatitis, and active cancer) within 1 year
- Participation in a patch test or soap chamber test within 4 weeks of the study
- Participation in a clinical trial or receipt of an investigation medication within 1 month of the study
- Routine use of anti-inflammatory, immunosuppressive or antihistamine medications
- Current use of allergy injections
- Use of systemic or topical anti-inflammatories or antihistamines within 72 hours of study enrollment, (subjects taking 81mg of aspirin for cardiovascular preventative were allowed to participate)
- Use of systemic or topical corticosteroids within 3 weeks of study enrollment
- Severe asthma, active immunologic disorders, insulin dependent diabetes, clinically significant chronic illness which could have placed the subject at increased risk during participation or resulted in an inappropriate dermal response during the study
- Alcohol or drug abuse within 1 year of the study
- Inability to provide written informed consent or judged by the investigator to be unsuitable for any reason

Evaluation variables:
The primary study variable was the contact sensitization potential of 10% OTG and placebo gel. The following scale was used to evaluate skin reactions during the induction period and challenge phase. A score was assigned when a clinically significant skin reaction was noted or ≥ 25% of the test site showed a skin response.

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Scoring system for skin response:

Skin Responses – numeric grades:

0	No visible reaction and/or erythema
+	Slight, confluent or patchy erythema
1	Mild reaction – macular erythema (faint, but definite pink)
2	Moderate reaction – macular erythema (definite redness, similar to a sunburn)
3	Strong to severe reaction – macular erythema (very intense redness)

Skin Responses – letter grades:

E	Edema – swelling, spongy feeling when palpated
P	Papule – red, solid, pinpoint elevation
V	Vesicle – small elevation containing fluid
B	Bulla reaction – fluid-filled lesion (blister)
S	Spreading – evidence of the reaction beyond the application area
W	Weeping – result of a vesicular or bulla reaction – serous exudate
I	Induration – solid, elevated, hardened, thickened skin

Skin Responses – additional observation grade:

g	Glazing
y	Peeling
c	Scab, dried film of serous exudate of vesicular or bulla reaction
d	Hyperpigmentation (reddish-brown discoloration of test site)
h	Hypopigmentation (loss of visible pigmentation at test site)
f	Fissuring – grooves in the superficial layers of the skin

Reviewer's comment*: According to the sponsor, the dermal scoring system is the standard measure for scoring in sensitization studies.*

Statistical considerations:

Sample size: The sponsor planned to enroll 240 subjects with a goal of 200 completers and a minimum of 80 subjects of each gender. This sample size is standard for a sensitization study.

Analysis populations: Clinical analysis and data tabulation for the skin sensitization evaluations was performed using the Per Protocol (PP) population, which included all randomized subjects who completed the study (received 9 induction applications each of test and control gels and whose challenge sites were evaluated at least twice (5 minutes and 24 hours after the removal of the challenge gauze pad). All other analyses were performed using the Safety population, which included all randomized subjects who received at least one dose of study drug.

Skin sensitization analysis: The interpretation of data was based on the pattern of reactivity of the test article during induction phase compared to the severity and persistence of the reaction(s) observed at Challenge. Increased reactivity noted during the first week of induction to test articles considered non-irritating or minimally irritating generally indicated a pre-sensitized condition. Comparable reactivity during the third week, if it appeared suddenly, was suggestive of the initiation of sensitization. Irritation generally developed more gradually and was resolved with a comparable sequence after test article removal. A narrative description of each reaction in the challenge phase was provided with the investigator's opinion as to whether such reactions were indicative of contact sensitization or irritation.

***Reviewer's comment**: Contact dermatitis falls into 2 main categories: irritant and hypersensitivity. Both involve inflammatory processes and can have similar clinical characteristics of erythema, induration, scaling, and vesiculation in areas of direct contact with the chemical. The pattern of response is important to differentiating whether a skin reaction is of irritation or allergic nature. The inflammatory response to contact irritants is gradual and proportional to the dose. Allergic contact dermatitis is a delayed, T-cell mediated hypersensitivity reaction. The memory T-cells are generated over a 1-3 week period. Upon re-exposure to the allergen, the inflammatory response is immediate and proportionally much larger than the dose.*

Subject Disposition:
A total of 225 subjects were enrolled and treated, and 200 subjects completed the study. The PP population included 200 subjects and the Safety population included 225 subjects. Twenty-five subjects withdrew prematurely: 6 due to adverse events, 5 due to protocol violation, 9 due to refusal/inability to participate further, and 5 were lost to follow-up. Although there were no major protocol violations, there were 469 minor violations. The most common minor violation included skin evaluations not conducted with in the allotted time periods or not conducted (n = 245 or 50%).

***Reviewer's comment**: A review of the line listing of protocol deviations by subject (study report, Appendix 16.2.23) showed that 6 patients had at least one missing evaluation or had an evaluation but a score was not recorded. Given the number of skin evaluations for each subject, this reviewer does not anticipate that these missing data would significantly alter the study findings.*

Demographics and baseline characteristics:
Subjects were primarily non-Hispanic (91%) White (87%) men (39%) and women (61%) with an average age of 42 years. The demographics were similar between the PP and Safety populations.

Skin sensitization results:
One subject experienced contact sensitization to the active gel (0.5%). Subject 1087 had mild erythema and papules at each of the challenge evaluations of the active OTG application site. Re-challenge was performed on Subject 1087 who again experienced mild erythema with papules on the OTG application site at the 5-minute, 24-hour, 48-hour, and 72-hour after the removal of the rechallenge gauze pad.

***Reviewer's comment**: This reviewer reviewed the line listing of dermatologic evaluations of all subjects. Subject 1020 had +P score (slight, confluent or patchy erythema; red, solid, pinpoint papules) after the 8th and 9th but did not have any skin reaction during the challenge phase. No other subjects had any significant trend of skin reactions in the Induction period and Challenge Phase.*

Skin tolerability results: The findings of skin tolerability in the Challenge phase and Induction period are summarized in Table 1 and Table 2.

Table 1: Dermal Evaluation Scores during Challenge Phase

Time after gauze removal	**5 Minutes**		**24 hours**		**48 hours**		**72 hours**	
Skin irritation Score*	Placebo N=201	OTG N=201	Placebo N=201	OTG N=201	Placebo N=200	OTG N=200	Placebo N=200	Gel N=200
0	190	187	198	193	198	199	197	195
+	10	13	3	5	1	0	1	2
1	1	1	0	3	1	1	0	1
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
Not scored (NS)	0	0	0	0	0	0	2	2

Source: Study report, tables 11.4.1.1-2 and 11.4.1.1-1, p. 23-24

*0=no visible reaction and/or erythema; +=slight, confluent or patchy erythema; 1=mild reaction, macular erythema (faint but pink); 2=moderate reaction macular erythema (redness similar to sunburn); 3=strong to severe reaction, macular erythema (very intense redness)

Table 2: Dermal Evaluation Scores during Induction Period

Application #	**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**9**	
N=201	P*	O*	P	O	P	O	P	O	P	O	P	O	P	O	P	O	P	O
+	8	9	14	17	13	13	9	9	8	8	2	4	5	5	5	6	10	8
1	0	2	1	4	1	7	1	2	0	0	0	0	0	0	0	1	1	2
2	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	1	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NS	0	0	1	1	1	0	0	1	0	0	0	0	1	1	0	0	2	1

*P=placebo; O=OTG
Source: Study report, tables 11.4.1.2-1 and 11.4.2.2-2, p. 25-26

***Reviewer's comment**: The skin tolerability assessment was based primarily on erythema changes at the application site. There were no moderate or severe reactions in the OTG group. During the Induction period, 2-8% of OTG application sites showed slight, confluent or patchy erythema (+) compared to 1-6% of placebo application sites. During the same period, 0-2% of OTG application sites showed mild reaction, macular erythema (score = 1) compared to 0-0.5% of placebo gel sites.*

Safety analysis:

- *Extent of exposure*: Two hundred and twenty five (225) subjects were enrolled in the study and received at least one dose of gel application. Two hundred and one (201) subjects received all 9 Induction applications and Challenge applications, and one subject received one re-challenge application. Twenty five (25) subjects were exposed to between 1 and 10 applications before discontinuing their participation in the study.

- *Adverse events*: 91 subjects (40.4%) reported a total of 148 adverse events. One death related to alcoholism and unrelated to treatment occurred (subject 1039). No other SAE was reported. Of the 25 subjects who discontinued prematurely, 6 withdrew because of an adverse event (2 subjects experienced diarrhea, one subject each experienced blurred vision, urinary tract infection, tape irritation at application sites, and death from complications of alcoholism). The most common adverse events were related to the application sites. Fifty-three (53) subjects reported 103 application site adverse events. Seven subjects reported 16 application site adverse

reactions (application site irritation, pruritus, and warmth). The distribution of the application site adverse reactions was similar between the placebo and active gel. Other adverse reactions included dry mouth (1), diarrhea (3), dry throat (1), abdominal cramps (1), blurred vision (1), and dizziness (1).

- *Pregnancy*: None

Reviewer's comment*: A review of the line listing of all adverse events was conducted. No unexpected AE's occurred.*

Reviewer's assessment: Under test conditions, one subject (0.5%) was sensitized to 0.5 g OTG 10% and none was sensitized to placebo gel.

10.1.4 Study OG06007

Study Title: "An evaluation of the person-to-person transference and absorption potential of oxybutynin following application of oxybutynin topical gel to healthy volunteers"

Study period: March 2007 – April 2007

Objective: To determine the potential of topically applied oxybutynin gel to be transferred between treated and untreated subjects by direct physical contact at the application site

Study design and conduct: This was a single-center, open-label, randomized, single dose, parallel group study evaluating the potential of person-to-person transference of 10% OTG. Subjects were randomized to receive one dose of 1 g 10% OTG applied to the abdomen (treated) or no treatment (untreated). The treated subjects were further randomized to cover the application site with clothing or remained unclothed during the physical contact with untreated subjects. At one hour post-application, the treated and untreated subjects engaged in direct physical contact (abdomen-to-abdomen) at the application site for 15 minutes. Blood samples for oxybutynin and N-desethyloxybutynin PK parameters were drawn from untreated subjects at 0 (before contact), 2, 4, 8, 12, 36 and 48 hours after the physical contact. Treated subjects provided one blood sample drawn 3 hours post-application to verify dosing. Adverse events were monitored.

Eligibility Criteria:
Inclusion:

- In general good health and aged 18 to 45 years
- Using a medically accepted contraceptive (women of childbearing potential only)
- BMI of 18-30 and weight ≥ 50 kg and ≤ 90 kg
- Provide written informed consent

Exclusion:

- Significant findings on physical exam
- Current acute or chronic medical therapy
- Clinically significant laboratory or ECG findings
- History of narrow angle glaucoma or urinary or gastric retention
- Pregnant or lactating
- Recent history (within last year) or current alcohol or drug abuse

- Tobacco use within past 6 months
- Dermatological diseases, skin damage or blemishes that may affect tolerability of gel or its assessment
- Blood donation within past 12 weeks
- Hypersensitivities, allergies, or contraindications to any component of the gel formulation
- Inability to comply with treatment schedule
- Participation in an investigational drug study within 30 days prior to the screening visit
- Excessive hair growth on the abdomen which would interfere with the application of the gel
- Judged by investigator to be unsuitable for enrollment

Study Variables:
The primary variables were plasma oxybutynin concentrations and the derived PK parameters ($AUC_{[0-48]}$, Cmax, Tmax) in the untreated subjects. Safety variables were adverse events, skin tolerability, and vital signs.

Statistical considerations:
All statistical analyses were descriptive in nature. The PK analyses were performed using the Evaluable population, which included all untreated subjects who completed the study, provided all plasma concentration data from each sampling time period, and who did not have any major protocol deviations. The Safety population included all treated subjects who received at least one dose of study drug and untreated subjects who participated in the physical contact with treated subjects.

Subject Disposition:
Fifty-two (52) subjects were enrolled in the study and 52 completed the study. The Evaluable population included 25 subjects; one untreated subject (1509-b) did not provide blood for all sample draws and was excluded. A review of PK findings of subject 1509-b, who participated in the skin-to-clothing contact regimen, indicated that the subject had not detectable oxybutynin plasma levels at any of the sampled time points. The Safety population included 52 subjects. No important protocol violation or the use of concomitant medications occurred that were felt to affect the study results.

Demographics and baseline characteristics: The Safety population consisted of 25 male and 27 female subjects with a mean age of 25 years (range 18-44 years). The Evaluable population was comprised of 11 male and 14 female subjects. All subjects were healthy and met all the eligibility criteria.

Person-to person transference results: All untreated subjects had measurable oxybutynin levels after direct skin-to-skin contact with treated subjects at the application site. Oxybutynin levels were detectable at the first blood draw post-contact (2 hours) and continued to be detectable 48 hours post-contact. The mean Cmax of 0.94 ng/mL occurred at approximately 18 hours after the skin-to-skin contact. Although drug transference occurred in both male and female untreated subjects, female subjects tend to absorb more drug and had higher mean Cmax oxybutynin concentrations than males. The PK findings are summarized in Table 1.

Table 1: Oxybutynin PK Parameters Following Skin-to-Skin Contact

PK Parameter	Statistic	Female subjects N=7	Male subjects N=6	All N=12
AUC $_{[0-48]}$ (ng.hr/mL)	Mean (SD)	37.7 (29.0)	18.7 (11.1)	29.8 (24.5)
	Min, Max	11.0, 85.7	9.4, 32.5	9.4, 85.7
Cmax (ng/mL)	Mean (SD)	1.14 (0.9)	0.7 (0.5)	0.94 (0.7)
	Min, Max	0.4, 2.3	0.3, 1.2	0.3, 2.3
Tmax (hr)	Mean (SD)	15.7 (8.1)	19.5	17.3
	Min, Max	8.3, 24.3	12.3, 24.3	8.3, 24.3

Source: Study report, Table 11-2, p. 25

***Reviewer's comment**: In other single-dose PK studies with 1 g 10% OTG; female subjects had slightly higher Cmax and AUC than male subjects. The differences appeared to be too small to be clinically significant.*

As a comparison, in Study OG04007 where healthy subjects received one dose of 1 g 10% OTG and PK parameters were evaluated for 144 hours post-application, the mean Cmax (ng/mL) was 4.7 ng/mL and the mean AUC (0-144) was 220 ng/mL. The median Tmax was approximately 20 hour post-application.

Twelve of the 14 untreated subjects participating in the skin-to-clothing contact (treated subjects covered the application site with clothing) had no detectable plasma oxybutynin levels at any of the sampled time points. Two subjects had measurable oxybutynin plasma levels starting at 8 hours post-contact. Both of these subjects were females. For subject 1508-b, Cmax was 0.07 ng/mL and AUC (0-48 h) was 1.86 ng/mL. For subject 1514-b, Cmax was 0.1 ng/mL and AUC (0-48 h) was 1.57 ng.h/mL

***Reviewer's comment**: A review of PK parameters of individual subjects was conducted.*

- *All untreated subjects participating in the skin-to-skin contact had detectable plasma oxybutynin levels indicating 100% potential for systemic absorption of OTG.*
- *Two untreated patients participating in the skin-to-clothing contact had detectable plasma oxybutynin levels. For subject 1508-b, Cmax occurred at 8 hours after contact. At the 48 hour time point, the plasma oxybutynin concentration was 0.05 ng/mL. For subject 1514-b, Cmax occurred at 8 hours after contact. Oxybutynin plasma levels were no longer detectable after 24 hours post-contact. The plasma oxybutynin levels of the treated partners of these 2 untreated subjects were similar to those of other treated subjects.*
- *The oxybutynin exposure levels observed in the 2 untreated subjects with detectable plasma oxybutynin were minimal and should not pose a significant safety concern except in patients with hypersensitivity to OTG or to oxybutynin. Covering the application site with clothing provided sufficient protection from person-to-person transference of OTG.*

Safety: Twenty six (26) subjects received one dose of 1 g 10% OTG, and 14 untreated partners were exposed to oxybutynin to a variable extent through physical contact with the treated subjects at the application site. One subject (1512-b) who was the untreated partner participating in the clothing-to-skin contact regimen reported one unrelated adverse event of mild myalgia. No other adverse events were reported.

Reviewer's assessment: 10% OTG is transferable from a treated person to an untreated partner through direct skin-to-skin contact at the application site. This risk can be sufficiently minimized by covering the application site with clothing.

10.1.5 Study OG06001

Study Title: "Plasma oxybutynin and N-desethyloxybutynin concentrations following application of 1 g 10% oxybutynin topical gel when co-administered with sunscreen at the same application site"

Study period: April 2006 – May 2006

Objective: To evaluate the effect of sunscreen on the rate and extent of absorption of oxybutynin when sunscreen was applied before and after applications of OTG. Secondary objectives included the evaluating of the effect of co-administration of OTG and sunscreen on the metabolism of oxybutynin, local skin tolerability, and adverse events.

Study design and conduct: This was a single center, 3-period, open-label, randomized crossover study of single dose applications of 1 g 10% OTG. Subjects received 3 treatments (OTG application alone, OTG application preceded by sunscreen application, OTG application followed by sunscreen application) in a randomized sequence with each subject receiving each study treatment once. There was a minimum 14-day washout between each treatment. During the treatment period where the OTG and sunscreen were both administered, the products were applied to the same site (abdomen) 30 minutes apart. Blood samples were collected for plasma oxybutynin and N-desethyloxybutynin levels prior to OTG application and 2, 6, 12, 16, 20, 24, 28, 48, and 72 hours following OTG application. Safety evaluations included monitoring of adverse events and skin tolerability (erythema scores) assessment. See Study Schedule.

Study Schedule:

	Days -14 to -2	Days -1,14,28	Days 1,15, 29	Days 2,16,30	Days 3,15,31	Days 4,18,32	Day 32/ ET
Informed consent	X						
Inclusion / exclusion	X						
Demographic Data	X						
Body Weight/Height	X						
Medical History	X						
Current Illness / Meds	X	X					
Vital Signs	X						X
Physical Examination	X						
ECG	X						
Clinical Lab Tests	X						
Urinalysis	X						
Drug Screen	X	X					
Pregnancy Test	X	X					X
Gel/Sunscreen Application			X				
Blood Samples			X	X	X	X	
Skin Tolerability			X	X			
Adverse Event Query			X	X	X	X	X
Confinement in Clinic			X	X			
Exit Study							X

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Source: Study report, Table 9-2, p. 16

***Reviewer's comment**: The sunscreen used in the study was a water-based, oil-free SPF 15 product. The dose of sunscreen used was 800 mg per each application based on the FDA guidance specification of application of 2 mg/cm2 of application surface area in studies evaluating sunscreen products (Over-the-Counter Drug Products Monograph on Sunscreens (Final Version). US Food and Drug Administration, Federal Register 1999: 64: 27666-27963).*

Eligibility Criteria:
Inclusion:

- In general good health and aged 18 to 45 years
- Using a medically accepted contraceptive (women of childbearing potential only)
- BMI of 18-30 and weight ≥ 50 kg and ≤ 90 kg
- Provide written informed consent

Exclusion:

- Significant findings on physical exam
- Current acute or chronic medical therapy
- Clinically significant laboratory or ECG findings
- History of narrow angle glaucoma or urinary or gastric retention
- Pregnant or lactating
- Recent history (within last year) or current alcohol or drug abuse
- Tobacco use within past 6 months
- Dermatological diseases, skin damage or blemishes that may affect tolerability of gel or its assessment
- Blood donation within past 12 weeks
- Hypersensitivities, allergies, or contraindications to any component of the gel formulation
- Inability to comply with treatment schedule
- Participation in an investigational drug study within 30 days prior to the screening visit
- Excessive hair growth on the abdomen which would interfere with the application of the gel
- Judged by investigator to be unsuitable for enrollment

Study Variables:
The primary variables were the PK parameters ($AUC_{[0-24]}$, $AUC_{[0-72]}$, Cmax, Tmax) derived from plasma oxybutynin and DEO concentrations. Safety variables included adverse events, skin tolerability, and vital signs.

Statistical considerations:
All statistical analyses were descriptive in nature. PK analyses were analyzed using the Evaluable population, which included all subjects who completed all 3 treatment periods and who did not have any major protocol violations. Safety analyses were analyzed using the Safety population, which included all subjects who received at least one dose of study drug.

Subject disposition: 16 subjects were enrolled and 14 subjects completed the study. One subject (1210) withdrew consent prior to Treatment Period 3, and one subject (1204) was withdrawn during Period 3 due to use of excluded medication. There were no major protocol violations.

Demographic and baseline characteristics: The Safety population comprised of 16 subjects (8 males, 8 females) with a mean age of 25.9 years (range 19 to 45 years). The Evaluable population consisted of 14 subjects (6 males, 8 females). All subjects were Caucasian and met the eligibility criteria.

Plasma oxybutynin and DEO concentrations and PK with OTG and sunscreen applications

The PK findings are summarized in Table 1.

Table 1: Oxybutynin PK Parameters by Treatment Regimen

PK Parameter	Statistic	OTG alone	Sunscreen/OTG	OTG/Sunscreen
AUC (0-72) (ng.h/mL)	Mean (SD)	84.5 (48.6)	91.2 (55.5)	83.6 (41.4)
	Min, Max	17.6, 167.0	26.2, 207.9	26.8, 166.2
Cmax (ng/mL)	Mean (SD)	2.7 (1.7)	3.01 (2.0)	3.02 (1.8)
	Min, Max	0.54, 5.5	0.7, 7.4	0.8, 6.4
Tmax (h)	Mean (SD)	23.4 (4.9)	25.7 (4.1)	23.7 (5.5)
	Min, Max	12, 28.0	20, 36	12, 36
DEO:OXY AUC $_{(0\text{-}72\ h)}$		0.82	0.86	0.78

Source: Study report, Table 11-2, p. 28

***Reviewer's comment**: Based on mean values, compared to OTG alone, applying sunscreen 30 minutes prior to OTG application resulted in a slight increase in AUC, Cmax, and Tmax. Applying OTG 30 minutes prior to applying sunscreen resulted in a slight increase in Cmax. These differences are not likely to result in clinically meaningful differences in safety.*

Safety:

- *Extent of exposure*: 16 subjects received at least one dose of study drug, and 14 subjects received all 3 doses of 1 g 10% OTG. Two subjects withdrew after receiving 2 applications. Subject 1210 did not return to the clinical for the third dosing period, and subject 1204 withdrew before dosing in Period 3 due to exclusionary concomitant medication use.

- Adverse events: Two subjects reported 2 adverse events. One subject reported a mild headache and another subject experienced allergic contact dermatitis after exposure to poison ivy. Neither one of these AE's were treatment-related.

- Skin tolerability: No subject experienced any erythema after any OTG application with or without sunscreen, and no subject reported any application site reaction.

Reviewer's assessment: Sunscreen administered 30 minutes before or after OTG application did not affect the PK or metabolism of OTG 10%.

11 REFERENCES

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NDA 22-204/S000

Medical Officer's 45-Day Filing Memorandum

Application Letter Date:	March 26, 2008
45-Day Filing Review Date:	May 11, 2008
Mid-Cycle Review Date:	August 27, 2008
Prescription Drug User Fee Act (PDUFA) Goal Date:	January 27, 2009
Related Submissions:	IND 67,126 (b) (4) NDA 21-351 (Oxytrol TDS)
Product, route and dose:	1 g 10% Oxybutynin Chloride Topical Gel topically once daily
Indication:	Treatment of Overactive Bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency

I. Summary

Objective:

This review assesses whether NDA 22-204 is suitable for filing under 21 CFR 314.50, Content and format of an application, and 21 CFR 314.71, Procedures for submission of a new NDA. This document also serves as the basis for communicating to sponsor potential clinical review issues identified during this initial review period.

Conclusion:

Following a preliminary review of one phase III study of efficacy and safety (OG05009) and 13 phase I studies, the draft label, and financial disclosures for investigators of Study OG05009, NDA 22-204 is fileable from a clinical perspective.

II. Background

Brief Regulatory History:

Oxybutynin Chloride Topical Gel 10% (OTG 10%) is an anticholinergic product developed by Watson Laboratories, Inc., as a topical gel formulation for once a day dosing for the treatment of OAB. The sponsor is seeking approval of this product for the "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." The proposed dose is one sachet containing 1 g of 10% oxybutynin gel (100 mg oxybutynin) once daily with no specific dose adjustments for specific populations. OTG 10% has not been approved for marketing in any country.

The sponsor opened IND 67,126 on March 21, 2003. An End-of-Phase 2 meeting was held with the sponsor on August 2, 2005, during which the Division "highly recommended" 2 phase III 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 to support marketing approval in a follow-up teleconference held on November 4, 2005, during which the following were discussed:

1. The sponsor planned to support approval with 1 phase III, statistically persuasive trial, with 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." Final action on an NDA would ultimately be a review issue.
3. The Division also stated that PK parameters must be sufficiently similar and this, too, would be a review issue.

A pre-NDA meeting was held with the sponsor on December 13, 2007, to discuss the submission of the NDA for OTG 10%.

III. NDA Filing Review

Filing Review: The review is based on three criteria proposed in FDA guidance for the filing review, based on the Agency's interpretation of 21 CFR 314.101 (d) (3) and 21 CFR 314.50.

1. Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner.
2. Failure to include evidence of effectiveness compatible with the statute and regulations.
3. Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Submitted materials:
The sponsor submitted the safety and efficacy data from 11 clinical pharmacology studies, 2 dermatoxicity trials, and 1 phase III safety and efficacy trial (see Table 1).

Table 1: Summary of clinical studies with OTG

Type of Study	Objective	Test product	Duration of treatment	# of subjects (M/F)
Phase I clinical pharmacology				Healthy subjects
OG02020	Bioavailability (BA) and pharmacokinetics (PK)	3 g 4.4% once daily	3 days	12 (10/2)
OG03013	Surface area of application on BA	3 g 4.4% single dose	2 days	22 (11/11)
OG03018	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose, 1 g 13.2% single dose	2 days	22 (10/12)
OG04004	Comparative BA and PK of 2 different formulations	3 g 4.4% single dose 1 g 13.2% single dose	2 days	20 (10/10)
OG04007*	Comparative BA and PK of 3 different OTG formulations and Oxytrol	3 g 4.4% single dose 1 g 10% single dose 3 g 10% single dose 3.9 mg/day Oxytrol single application (one TDS for 3.5 days)	6.5 days	22 (13/9)

OG03005	Steady state BA and PK	3 g 4.4% once daily	8 days	20 (11/9)
OG04008*	Steady state PK and application site bioequivalence	1 g 10% once daily	42 days	40 (20/20)
OG06005*	Steady state PK and comparison with Oxytrol	1 g 10% once daily Oxytrol x 4 applications (each application = 3.5 days)	36 days	22 (12/10)
OG06001*	Effect of sunscreen	1 g 10% single dose	3 days	16 (8/8)
OG06006*	Effect of showering	1 g 10% once daily	35 days	20 (9/11)
OG06007*	Transfer potential	1 g 10% single dose	1 day	52 (25/27)
Dermatoxicity studies				Healthy subjects
OG05003*	Cumulative irritation	1 g 10% once daily 1 g placebo once daily	21 days	45 (14/31)
OG05004	Skin sensitization	0.5 g 10% three times per week for 3 weeks 0.5 g placebo gel 3 times per week for 3 weeks	22 days	225 (87/138)
Phase III safety and efficacy				OAB patients
OG05009-double blind*	Safety and efficacy of 1g 10% OTG in target population	1 g 10% once daily 1 g placebo once daily	12 weeks	789 389 OTG (37/352) 400 plac (48/352)
OG05009-open label*	Safety	1 g 10% once daily	14 weeks	216 (22/194)

*Studies using the to-be-marketed dose and formulation (1 g 10% OTG)
Source: Synopses of Individual Studies, Module 2.7.6, Table 2.7.6-1, p. 4-6

REVIEW RESULTS

1. ***Does this amendment omit a section required under CFR 314.50, or was a particular section presented in such a manner as to render it incomplete for the clinical review?***

Response: No.

This NDA contains the critical sections in sufficient detail (see Table 2 and Appendix A).

TABLE 2: Checklist for critical sections

Comprehensive table of contents	Yes
Summary of the application	Yes
Technical sections (CMC, pharmacology/toxicology, clinical pharmacology, clinical)	Yes
Case report forms and tabulations	Yes

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2. ***Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:***
    a. ***Lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints***
    b. ***Presentation or what appears to be only a single adequate and well controlled trial without adequate explanation***
    c. ***Use of a study design clearly inappropriate***

Response: No.

The following section of the filing review summarizes the efficacy findings of one phase III study (OG05009) with an open-label extension. All clinical efficacy data were obtained from the double-blind phase of Study OG05009.

Reviewer's comment: *The sponsor is seeking approval of a new dose and formulation of oxybutynin, an active moiety with extensive clinical experience in the target population. Study OG05009 was a large, multicenter study that appears to have internal consistency of study findings and strength of statistical results. Although concentration-response for oxybutynin and its metabolite, desethyloxybutynin, is not well characterized, the pharmacokinetic of OTG 10% appears to be similar to that of an approved oxybutynin transdermal system, Oxytrol. Taken all together, a single confirmatory study should provide sufficient evidence to support filing of this NDA.*

2.1 Study design of OG05009

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study in OAB patients. The study consisted of 3 periods: 4-week screening, 12-week double-blind (DB) period, and 14-week open label (OL) extension. Patients with $\geq$ 4 urge urinary incontinence episodes (pure urge or mixed urinary incontinence with a predominance of urge incontinence) in 3 days and $\geq$ 8 urinary voids per day as recorded in a 3-day baseline urinary diary and whose OAB symptoms were not related to chronic illness, anatomical weakness, or medication use were eligible for enrollment. Enrolled patients were randomized in a 1:1 manner to either 1 g 10% OTG or matching 1 g placebo gel applied topically once daily on an alternating basis to the abdomen, shoulder/upper arms, or thighs. Three patient populations were used in the analysis of efficacy: the modified intent-to-treat (mITT), which included all patients who received at least one dose of study drug and provided data for the baseline efficacy assessment, ITT (same as mITT except in cases of misrandomization, the patient was grouped by the randomized treatment and not the actual treatment received), and Evaluable (mITT population who were without major protocol violation, completed 12 weeks of treatment, and provided data for the primary efficacy endpoint at Visit 7/Week 12). The mITT population was the primary analysis population. Missing data would be handled by the last-observation-carried-forward (LOCF) method.

Primary Endpoint was change from baseline (CFB) in the average number of urinary incontinence episodes per day to Endpoint Last Observation Carried Forward (LOCF).

Key secondary endpoints included CFB in average daily urinary frequency and urine volume per void to Endpoint (LOCF).

Open-label extension: Eligible patients from selected study sites who completed the 12-week treatment period were enrolled in the 14-week open label extension. The primary objective was to evaluate skin safety of OTG 10% use for 6 months. No efficacy outcomes were assessed other than incontinence-specific quality of life evaluations.

Reviewer's comment: *The Division agreed to the statistical analysis plan in a letter dated September 20, 2007. The overall protocol is acceptable.*

2.2 Patient disposition and baseline characteristics of OG05009

Study OG05009 was conducted at 76 centers throughout the U.S. The trial enrolled and randomized 789 patients (389 to OTG 10% and 400 to placebo). Of these 789 patients, 701 (88.8%) patients completed the 12-week DB period. Similar proportion of patients on OTG (11.1%) and placebo (11.3%) discontinued prematurely during the DB period.

The average age of both treatment groups was 59.4 years with an average duration of incontinence of 8.5 years. Approximately 90% of patients in both treatment groups were females with a similar proportion being Caucasian. The mean (SD) number of daily urinary incontinence episodes at baseline was similar between the OTG group [5.4 (3.28)] and placebo group [5.4 (3.26)]. Approximately 64% of patients in each treatment group experience stress urinary incontinence at baseline. Other baseline characteristics, including geriatric status, body mass index (BMI), concomitant medications, proportion of patients with neurogenic cause of urinary incontinence, daily urinary frequency, and average urine volume per void were balanced between the 2 study groups. Slightly more placebo patients used pharmacologic treatment for OAB (27.3%) than OTG patients (23.4%).

2.3 Efficacy Findings of OG05009

2.3.1 Primary endpoint:

The OTG group experienced a statistically significant decrease in the number of urinary incontinence episodes per day from baseline to Endpoint (LOCF) compared with placebo ($p < 0.0001$). At Endpoint (Week 12/LOCF), the mean number of incontinence episodes in the OTG group decreased by 3.0 episodes per day compared with 2.5 per day for placebo (see Table 3). The difference in change from baseline in the number of incontinence episodes was statistically significant between OTG and placebo from Week 4 to Week 12. Similar results were obtained using the ITT and Evaluable populations and the OC dataset.

Table 3: Daily urinary incontinence episodes at baseline and change from baseline to Endpoint (mITT, LOCF)

Daily urinary incontinence episodes	Statistics	Placebo N=400	OTG N=389
Baseline	Mean (SD) Median	5.4 (3.28) 4.7	5.4 (3.26) 4.7
Endpoint change from baseline (LOCF)	Mean (SD) Median p-value	-2.5 (3.06) -2.0	-3.0 (2.73) -2.7 **<0.0001**

Source: Study report, Table 11-6, p. 61

Reviewer's comment: *The magnitude of treatment effect of OTG 10% appears modest (mean treatment difference -0.5 episode/day). This treatment effect, however, is more or less similar to those observed with some other approved medical treatment of OAB (see Table 4).*

Table 4: Treatment effect of other OAB products

Products	Placebo	Drug	Comments
Oxytrol TDS #incontinence episodes per day Mean (SD) Baseline Mean (SD) change from baseline	 5.0 (3.2) -2.1 (3.0)	 4.7 (2.9) -2.9 (3.0)	*Mean treatment difference: -0.8 episode/ day*
Detrol LA- # incontinence episodes per week Mean Baseline Mean change from baseline	 23.3 -6.9	 22.1 -11.8	*Treatment difference: -4.8 (-6.9, -2.8) episodes per week (-0.69 episode/day)*
Enablex (darifenacin) 7.5 mg* # incontinence episodes per week Median Baseline Median change from baseline	 16 -6 to -9	 16 -8 to -9	*Treatment difference: -1.5 to -2.8 episodes per week (-0.2 to -0.4 episode/day)*

*The recommended starting dose for Enable is 7.5 mg once daily and may be increased to 15 mg as needed.
Source: Oxytrol TDS, Detrol LA product labels

2.3.2 Secondary endpoints:

- Daily urinary frequency: The baseline number of micturition per day was approximately 12 for active and placebo groups. At Endpoint, the OTG group experienced a statistically significant decrease from baseline in the average daily urinary frequency compared to the placebo group (p=0.0017). The mean decrease in urinary frequency was 2.7 episodes for the OTG group and 2.0 episodes for the placebo group.
- Average urine volume per void: Mean baseline for the average urinary volume per void was 163 mL for placebo group and 168 mL for the OTG group. OTG treatment resulted in a statistically significant increase in the average urinary void volume at Endpoint compared to placebo (p=0.0018). The mean (SD) change from baseline was 21.0 mL (65.33) for OTG and 3.8 mL (53.79) for placebo.

Reviewer's comment*: Interpretation of statistical significance for secondary endpoints is considered exploratory and may not be included in the label.*

2.4 Preliminary efficacy conclusions

- After a preliminary review, treatment with OTG appears to result in a statistically significant improvement in the number of urinary incontinence episodes (primary endpoint) in the target population. The findings of the key secondary endpoints were supportive of the findings of the primary endpoint.
- The clinical significance of the treatment effect of OTG will be a review issue.

3. ***Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:***
    a. ***total patient exposure at relevant doses that is clearly inadequate to evaluate safety***
    b. ***clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets***
    c. ***absence of a comprehensive analysis of safety data***
    d. ***absence of an analysis of data supporting the proposed dose and dose interval***

Response: No.

3.1 Safety Exposure

In total, the NDA contains safety data from 1033 subjects exposed to active OTG, which included 496 OAB patients in the integrated phase 3 study (double blind and open-label), 216 healthy subjects in the integrated phase I studies, and 296 healthy subjects in the non-integrated phase I studies. During the DB and OL phase 3 study, 496 patients (389 in the DB period + 107 randomized to placebo in the DB period and received active OTG during the OL period) were exposed to 1 g 10% OTG for an average of 103 days (range 1-227 days). A total of 373 patients were exposed to OTG at least 12 weeks, and 71 patients were exposed to OTG for at least 26 weeks. In the integrated phase I studies, 118 subjects were exposed to 1 g 10% OTG, 116 subjects to 3 g 4.4% OTG, 41 subjects to 1 g 13.2% OTG, and 21 subjects to 3 g 10% OTG. Exposure in these studies ranged from 1 to 42 days. In the non-integrated cumulative irritation study (OG05003), 45 healthy subjects received daily applications of 1 g 10% OTG for 21 days. In the non-integrated sensitization study (OG05004), 225 healthy subjects received 0.5 g 10% OTG three times a week for 3 weeks followed by a single 24-hour challenge application. In the non-integrated transference study (OG06007), 26 healthy subjects received one dose of 1g 10% OTG.

Reviewer's comment:

1. *It appears that 1008 subjects (496 OAB patients in the DB and OL periods of the phase 3 study + 216 healthy subjects in the 10 integrated phase I studies + 296 healthy subjects in the 3 non-integrated studies), and not 1033 as stated by the sponsor, were exposed to active OTG.*
2. *In total, 578 subjects were exposed to the to-be-marketed dose/formulation 1 g 10% OT and 71 patients were exposed to 6 months of active treatment. Although these exposure numbers are less than those recommended by the ICH guidelines for a chronically administered drug, the safety profile of systemic oxybutynin is well known and safety exposure is adequate to evaluate skin safety.*
3. *One-hundred seventy eight (178) subjects were exposed to doses higher than the to-be-marketed dose (100 mg oxybutynin), although 80% of these subjects received single dose exposure.*
4. *Although safety data from 10 phase I studies and 1 phase III study were summarized in the Integrated Summary of Safety (ISS), the sponsor presented the data of the integrated phase I studies separately from those of the phase III study. This approach is acceptable because the*

study design, dose, exposure duration, and patient population differed significantly between the phase I and phase III studies. Three 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.

5. *Overall, the quantity and duration of patient exposure was adequate.*

3.2 Patient Demographics

The demographics of the OAB patients are shown in Table 5.

Table 5: Demographics of OAB Patients in DB phase III study

Characteristics	1 g 10% OTG N=389 N (%)	Placebo N=400 N (%)
Age		
< 65 years	246 (63.2)	260 (65)
≥ 65 years	143 (36.8)	140 (35)
Gender		
Male	37 (9.5)	48 (12)
Female	362 (90.5)	352 (88)
Race		
Asian	6 (1.5)	7 (1.8)
American Indian	2 (0.5)	1 (0.3)
Black	33 (8.5)	54 (13.5)
White	346 (89)	335 (84)
Multi-races	2 (0.5)	3 (0.8)
BMI (kg/m^2) (mean [SD])	31.01 (7.2)	31.5 (8)

Source: Summary of Safety, Module 2.7.4, Table 2.7.4-5, p. 13

Subjects in the integrated phase I studies consisted of an approximately equal number of healthy male and females, most of whom were White (90%), with an average age of 26 years (none were ≥ 65 years old), and a mean BMI of 24 kg/m^2. All 322 subjects enrolled in the non-integrated studies were healthy subjects, 61% of who were female, between the ages of 18 to 65 years.

Reviewer's comment: *The phase III study population was similar to those of other approved OAB products and consisted primarily of older, White women.*

3.3 Dose Rationale

The dose selection for Study OG05009 was based on PK studies demonstrating that 1 g 10% OTG, which delivered approximately 100 mg oxybutynin to systemic circulation, produced similar plasma drug and metabolite concentrations as Oxytrol transdermal system (3.9 mg/day).

Reviewer's comment*: The dose selection is based on pharmacokinetics and safety data and not on efficacy data.*

3.4 Specific Populations

Age, Gender, and Body Weight: No PK study was conducted to specifically evaluate factors. Available data from the phase III study did not indicate clinical differences in the PK or safety of

OTG based on age. The number of male patients was too small to draw meaningful conclusions. A rigorous evaluation of safety by body weight has not been performed.

Race: No specific PK study was conducted to investigate the effect of race. The number of non-Caucasian patients in the phase III study was too small to draw meaningful conclusions.
Geriatric: 38% of patients in the phase III study were ≥ 65 years old. No differences in safety or efficacy were identified between these patients and younger ones.

Pediatric: No pediatric study has been conducted with OTG.

Renal Impairment: No study has been conducted with OTG.

Hepatic Impairment: No study has been conducted with OTG.

Reviewer's comment: *Given that oxybutynin has been marketed for over 30 years, this reviewer does not anticipate any unexpected safety signals in the specific populations discussed above, with the exception of pediatric, with the OTG formulation.*

3.5 Safety Results

3.5.1 Adverse Events

The summaries of safety findings are presented in Tables 6–9. For the remainder of this review, the treatment group with "**< 12 weeks**" OTG exposure includes 1) patients randomized to OTG during the DB period who did not enroll in the safety extension and 2) patients randomized to placebo in the DB period who enrolled in the safety extension. The treatment group "**≥ 12 weeks**" exposure includes only patients randomized to OTG during the DB phase who enrolled in the safety extension.

Table 6: Double-Blind phase III study

Assessment	OTG N=389 Mean exposure = 81.5 days N (%)	Placebo N=400 Mean exposure = 81.5 days N (%)
Any adverse event Drug-related Severe	221 (57) 73 (19) 16 (4)	193 (48) 45 (11) 16 (4)
Serious AE (no deaths)	7 (1.8)	10 (2.5)
Discontinuation Drug-related	19 (4.9) 7 (1.8)	13 (3.3) 7 (1.8)
Application site reactions Leading to discontinuation	21 (5.4) 3 (0.8)	4 (1) 1 (0.3)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 13, p. 28

Table 7: Open-label phase III study

Assessment	OTG N=216 Mean exposure = 81.5 days N (%)
Any adverse event Drug-related Severe	97 (45) 22 (10) 9 (4.2)
Serious AE	0
Discontinuation Drug-related	15 (6.9) 11 (5.1)
Application site reactions Leading to discontinuation	13 (6.0) 9 (4.2)

Source: Study report, Table 12-3, p. 79

Table 8: Double-blind and open-label phase III study

Assessment	OTG < 12 weeks N=387 Mean exposure = 82.0 days N (%)	OTG ≥ 12 weeks N=109 Mean exposure = 177.3 days N (%)
Any adverse event Drug-related Severe	218 (56) 69 (18) 18 (5)	70 (64) 22 (20) 6 (6)
Serious AE (no deaths)	6 (1.6)	1 (0.9)
Discontinuation Drug-related	27 (7) 13 (3.4)	7 (6.4) 5 (4.6)
Application site reactions Leading to discontinuation	24 (6.2) 8 (2.1)	9 (8.3) 4 (3.7)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 14, p. 29

Table 9: Integrated phase I studies

Assessment	1 g 10% OTG N=118 Mean exposure = 23.1 days N (%)	3 g 10% OTG N=21 Mean exposure = 1.0 day N (%)	Other OTG* N=116 Mean exposure = 2.9 days N (%)	Oxytrol TDS N=43 Mean exposure = 11 days N (%)
Any adverse event Drug-related Severe	36 (31) 29 (25) 0	2 (10) 2 (10) 0	38 (33) 27 (23) 0	15 (35) 15 (35) 0
Application site reactions Leading to discontinuation	2 (1.7) 0	0 0	4 (3.4) 0	13 (30) 0
Serious AE	0	0	0	0
Discontinuation Drug-related	2 (1.7) 0	0 0	1 (1) 0	0 0

*Other OTG includes 3 g 4.4% and 1 g 13.2% dose/formulation

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 12, p. 27

Reviewer's comment:

- *No clinically significant differences in safety were noted between different groups of comparison.*
- *The utility of the integrated safety data from the phase I studies is limited due very dissimilar exposure duration.*

Serious Adverse Events

Deaths: One death occurred in the safety database. A 54 year-old female subject (subject 1039) participating in the skin sensitization study (OG05004) received 4 applications of OTG and was 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, gastrointestinal [GI] bleed) according to a medical examiner's autopsy report. The death was not considered to be treatment-related.

Non-fatal SAE's: No subject experienced a non-fatal SAE in the 10 integrated phase I studies or in the 3 non-integrated studies. In the phase III study, 17 patients experienced 18 SAE's (7 subjects in the OTG group reported 7 SAE's and 10 patients in the placebo group reported 11 SAE's). SAE's in the OTG group were non-cardiac chest pain, multiple myeloma, enlarging ovarian adenoma, atrial fibrillation, pneumonia, cerebral infarction, and osteoarthritis. None of the SAE's was considered treatment-related.

Seven patients discontinued the study as a result of the SAE's-3 subjects in the OTG group due to enlarging ovarian adenoma, atrial fibrillation, and cerebral infarction (1 each) and 4 subjects in the placebo group due to atrial fibrillation, labyrinthitis, vertigo, and joint dislocation (1 each). Other than vertigo, all SAE's leading to study drug discontinuation resolved.

Reviewer's comment: *This reviewer conducted a preliminary review of all SAE case narratives and did not consider any SAE to be treatment-related.*

Adverse Events Leading to Discontinuation

Phase III study: Overall, 47 of 789 patients (6.0%) withdrew from the study due to adverse events; 3.3% (13 of 400) placebo-treated patients and 6.9% (34 of 496) OTG-treated patients withdrew prematurely due to AE's. The most common drug-related AE's leading to premature discontinuation were application site AE's (13 or 2.4% on OTG, 1 or 0.25% on placebo), ranging from mild itching and erythema to severe rash and urticaria.

- Double-blind phase: 19 of 389 patients (4.9%) discontinued OTG and 13 of 400 patients (3.3%) discontinued placebo due to an adverse event. The primary reasons for discontinuations was application site reactions (4 patient in OTG group, 1 patient in placebo group), followed by headache (4 patients in OTG, 5 in placebo). The rate of discontinuation due to a treatment-related adverse event was identical between active and placebo groups (1.8%).
- Open-label phase: 15 of 216 patients (6.9%) discontinued prematurely due to an adverse event. A majority (9 patients, 4.1%) of discontinuations were due to application site AE's.
- Double-blind and open-label phases (comparison based on duration of treatment): Discontinuation rates due to an adverse event were similar for subjects exposed to < 12 weeks (7.0%) and those exposed ≥ 12 weeks of OTG treatment (6.4%). The discontinuation rates due to a treatment-related adverse event was higher in patients exposed to ≥ 12 weeks (4.6%) compared to those exposed < 12 weeks (3.4%). The most common events leading to discontinuation, application site adverse events, was higher

for subjects treated ≥ 12 weeks of treatment compared to those treated for < 12 weeks (3.7% versus 2.1%). The second most common reason for discontinuation was headaches. Treatment-related adverse events leading to premature discontinuation in OTG-exposed patients in the phase III study are shown in Table 10.

***Reviewer's comment**: With regard to premature discontinuations, the sponsor only submitted case narratives for the 7 patients who discontinued because of an SAE in the phase III study. The sponsor should provide case narratives for the remaining 40 patients who withdrew from the phase III study.*

Table 10: Treatment-related adverse events leading to premature discontinuation in double-blind and open-label phase III study

Preferred Term	OTG N=496 N (%)	Placebo N=400 N (%)
Application site reactions*	5 (1)	1 (0.2)
Application site dermatitis	3 (0.6)	0
Headache	3 (0.6)	3 (0.8)
Application site pustules	2 (0.4)	0
Dry eye	1 (0.2)	0
Abdominal distension	1 (0.2)	0
Constipation	1 (0.2)	1 (0.3)
Liver function test abnormal	1 (0.2)	0
Hypertonic bladder	1 (0.2)	0
Eye discharge	0	1 (0.2)
Rash	0	1 (0.2)

*Includes application site dryness, erythema, papules, pruritis, urticaria
Source: Study report, Table 14.3.1-10, Part 2

***Reviewer's comment**: According to the sponsor, skin tolerability scores for patients who discontinued because of application site AE's were "most commonly indicative of no erythema," which suggested that lack of erythema does not necessarily indicate acceptable skin tolerability. Furthermore, application site pustules, papules, and hives could be skin sensitization reactions.*

Integrated phase I studies: 3 of 216 subjects (1.4%) discontinued due an adverse event (1 each for puncture site hematoma, urinary tract infection, and vomiting), none of which were considered related to treatment.

Non-integrated studies: 8 of 322 subjects (2.5%) discontinued prematurely due to an adverse event. Five subjects had AE's considered to be treatment-related (2 moderate diarrhea, 1 mild blurred vision, 1 application site irritation, 1 application site pruritis). One subject each withdrew due to urinary tract infection, lower back pain, and alcoholism (death); these AE's were not considered treatment-related.

Treatment Emergent Adverse Events

Data from DB phase III, OL phase II, DB and OL phase III, and integrated phase I studies are presented in Tables 11-16. The most common adverse events and adverse reactions were related to anticholinergic effects, especially dry mouth, and application site reactions.

Table 11: Common treatment-emergent adverse events (> 2% for OTG and greater than placebo) for double-blind phase III study (Safety Population)

Preferred Term	1g 10% OTG N=389 N (%)	Placebo N=400 N (%)
Dry mouth	29 (7.5)	11 (2.8)
Urinary tract infection	27 (7)	17 (4.3)
Upper respiratory tract infection	21 (5.4)	20 (5)
Dizziness	11 (2.8)	4 (1)
Nasopharyngitis	11 (2.8)	9 (2.3)
Application site pruritus	8 (2.1)	3 (0.8)
Fatigue	8 (2.1)	4 (1)
Gastroenteritis viral	8 (2.1)	7 (1.8)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 16, p. 31

Reviewer's comment: *No unexpected adverse events were noted based on the known safety profile of oxybutynin. Dry mouth, dizziness, and application site pruritis are most likely to be treatment mediated and should be presented in product labeling. The higher incidences of upper respiratory tract infection, nasopharyngitis, and viral gastroenteritis in the active treatment group are unlikely to be treatment-related. It is unclear if urinary tract infection and fatigue are anticholinergic effects. There were no cases of somnolence in the phase III study.*

Table 12: Common treatment-related adverse events (≥ 1% in OTG group) in double-blind phase III study (Safety Population)

Preferred Term	OTG N=389 N (%)	Placebo N=400 N (%)
Dry mouth	27 (6.9)	11 (2.8)
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)
Constipation	5 (1.3)	4 (1.0)
Dizziness	6 (1.5)	2 (0.5)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 17, p. 32

Table 13: Common treatment-emergent adverse events (≥ 2%) open-label phase III study (Safety Population)

Preferred Term	OTG N=216 N (%)
Urinary tract infection	19 (8.8)
Upper respiratory tract infection	10 (4.6)
Application site dermatitis	5 (2.3)
Application site pruritus	5 (2.3)
Urine analysis abnormal	5 (2.3)

Source: Study report, Table 12-7, p. 82

Table 14: Common treatment-related adverse events (≥ 1%) in open-label phase III study (Safety Population)

Preferred Term	OTG N=216 N (%)
Application site dermatitis	5 (2.3)
Application site pruritis	5 (2.3)
Application site dryness	4 (1.9)
Dry mouth	4 (1.9)
Application site erythema	3 (1.4)

Source: Study report, Table 12-8, p. 82

Table 15: Common treatment-emergent adverse events (> 2% for subjects treated ≥ 12 weeks and incidence rates in subjects treated ≥ 12 weeks greater than those treated < 12 weeks) for double-blind and open-label phase III study (Safety Population)

Preferred Term	OTG ≥ 12 weeks N=109 N (%)	OTG < 12 weeks N=387 N (%)
Urinary tract infection	10 (9.2)	34 (8.8)
Upper respiratory tract infection*	10 (9.2)	19 (5)
Headache	8 (7.3)	13 (3.4)
Diarrhea	5 (4.6)	7 (1.8)
Nasopharyngitis*	5 (4.6)	10 (2.6)
Sinusitis*	5 (4.6)	8 (2.1)
Gastroenteritis viral*	4 (3.7)	7 (1.8)
Cough	4 (3.7)	2 (0.5)
Blood triglyceride increased*	4 (3.7)	1 (0.3)
Application site pruritus	3 (2.8)	10 (2.6)
Application site dermatitis	3 (2.8)	8 (2.1)
Bronchitis*	3 (2.8)	8 (2.1)
Fatigue	3 (2.8)	5 (1.3)
Dyspepsia	3 (2.8)	4 (1)
Influenza*	3 (2.8)	4 (1)
Pruritus	3 (2.8)	4 (1)
Hypertension*	3 (2.8)	3 (0.8)
Arthralgia*	3 (2.8)	2 (0.5)

*No cases were considered by investigator to be treatment-related

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 18, p. 32-33

Reviewer's comment: *Application site pruritus and dermatitis do not appear to increase significantly with longer duration of OTG exposure. No other adverse findings, other than headache, increased significantly with increasing duration of use.*

Table 16: Treatment emergent adverse events ≥ 2% for integrated phase I studies

Preferred Term	Overall OTG N=215 N (%)	Oxytrol TDS N=43 N (%)
Headache	29 (13.5)	1 (2.3)
Dry mouth	13 (6)	0
Dizziness	9 (4.2)	0
Nausea	10 (4.7)	1 (2.3)
Thirst	9 (4.2)	0
Vomiting	6 92.8)	0
Pyrexia	6 (2.8)	0
Application site pruritus	5 (2.3)	4 (9.3)

Source: Module 5.3.5.3, Integrated Summary of Safety, Table 15, p. 30

Severity: 3 patients in the DB phase III (2 OTG patients-headaches; 1 placebo patient-sinusitis) and 4 patients in OL phase III (3 application site AE's, 1 dry mouth) had drug-related AE's of severe intensity.

Non-integrated studies:

1. Cumulative irritation study (OG05003): 21 of 45 subjects (47%) experienced 34 AE's. Ten of these AE's were considered to be treatment related: 8 subjects reported 8 AE's of application site pruritis, 1 subject reported on AE of application site rash, and 1 subject reported one AE of application site pain.
2. Repeat insult sensitization study (OG05004): 91 of 225 subjects (40%) experienced 148 AE's. There was one fatal SAE in a 54 year-old female subject (subject 1039). She was lost to follow-up after 4 applications of OTG and placebo and was later found to have died from causes related to alcoholism (alcohol blood level of 0.09%, ketoacidosis, GI bleed), according to a medical examiner's autopsy report. Treatment-related AE's included application site pruritis (5 subjects), application site warmth (4 subjects), diarrhea (3 subjects), blurred vision (1 subject), abdominal pain (1 subject), dry mouth (1 subject), dry throat (1 subject), and non-application site pruritis (1 subject).
3. Transfer potential study (OG06007): 1 of 52 subjects experienced an adverse event (myalgia).

3.5.2 Skin Tolerability Assessments

Integrated Studies: Skin tolerability assessment was conducted in the integrated phase I and phase III studies and was based on visual inspection of the application site usually 1 and/or 24 hours after gel application. Tolerability was rated on a 4-point erythema scale of 0 (none), 1 (mild=faint erythema), 2 (moderate=bright pin/sunburned appearance), and 3 (severe=beet red appearance). Adverse skin reactions were also collected as adverse events during Phase III study. Results are presented in Tables 14 to 16.

Integrated Phase I studies:

Table 17: Erythema evaluation in integrated phase I studies

Erythema evaluation	All OTG Erythema events/total # of evaluations (%)	Oxytrol TDS Erythema events/total # of evaluations (%)
Mild		
1 hr	0/372	8/41 (20)
24 hr	1/565 (0.2)	4/41 (9.8)
Moderate		
1 hr	0	0
24 hr	0	1/41 (2.4)
Severe		
1 hr	0	1/41 (2.4)
24 hr	0	0

Phase III study:

Skin adverse events: During the DB phase III study, 21 patients (5.4%) on OTG and 4 patients (1%) on placebo reported application site AE's. During the OL phase III study, 13 patients (6%) reported at least one application site AE.

Erythema assessment

In the DB phase III study, 1466 and 1495 application sites were evaluated in the OTG and placebo groups, respectively. Fourteen (1.0%) evaluations in the OTG group had mild erythema compared to 13 (0.9%) in the placebo group. Five (0.3%) evaluations in the OTG group showed moderate erythema compared to none in the placebo group.

In the DB and OL phase III study, a total of 1634 application site evaluations were performed in the group with < 12 weeks exposure and 620 in the group with ≥ 12 weeks of exposure. In the group with < 12 weeks of exposure, 15 evaluations (0.9%) showed mild erythema and 4 (0.2%) showed moderate erythema. In the group with ≥ 12 weeks of exposure, 6 evaluations (1.0%) showed mild erythema and 2 (0.3%) showed moderate erythema.

Reviewer's comment:

- *There were no cases of severe erythema in the entire safety database with OTG use.*
- *Erythema changes did not appear to worsen significantly with longer duration of drug exposure.*
- *Skin tolerance of OTG appears to be better than that of Oxytrol TDS. In the phase III study with OTG, 6.7% patients reported application site adverse events compared to 23% of patients in the pivotal trials with Oxytrol. In the OTG group, 2.4% of patients discontinued due to skin adverse events compared to 7-9% of patients in the Oxytrol trials.*

Non-Integrated Dermatoxicity studies:

Study OG05003 (cumulative skin irritation study): This was a multiple dose, 21-day cumulative skin irritation study comparing active to placebo OTG gel (1 g 10% dose) in 45 subjects. The findings of the study did not indicate that OTG gel product is an experimental irritant.

Study OG05004 (skin sensitization study): This was a multiple dose, repeat insult sensitization comparison of active and placebo OTG (0.5 g 10% dose) in 225 subjects. One subject was sensitized to OTG 10%. Subject 1087 experienced mild erythema with papules at each of the

challenge evaluations on the OTG application site. During re-challenge, the subject had mild erythema with papules on the OTG application site at 5-minute, 24-hour, 48-hour, and 72-hour post-removal evaluations.

Study OG06007 (transference study): no application site evaluation was conducted.

***Reviewer's comment**: Allergic contact sensitivity to OTG 10% should be adequately labeled in the Warnings and Precaution section of the label. However, this finding is a review, and not a filing, issue.*

3.5.3 Laboratory findings

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were evaluated at baseline and at end of the study in the phase 3 study and in phase I study OG02020. Only results from Study OG05009 are discussed below.

Measures of central tendency: There were no significant differences in laboratory parameters (hematology or chemistry) with respect to mean laboratory values at baseline, at endpoint, and in changes from baseline between active treatment and placebo groups. Descriptive summaries did not reveal significant differences in the mean hematology values between patients with < 12 weeks OTG exposure and those with ≥ 12 weeks exposure.

Shifts from normal to abnormal: The proportion of patients with shifts from normal to abnormal (high or low) did not differ significantly between placebo and active treatment groups in the double-blind phase III study. During the open-label phase III study, the proportion of patients with shifts outside the normal range did not differ significantly between patients randomized to placebo during the double-blind period (maximum exposure 12 weeks OTG) and those randomized to OTG (maximum exposure 26 weeks OTG). See Table 18.

Table 18: Proportion of patients with normal baseline and an abnormal Endpoint value during double-blind phase (baseline to Visit 7/ET) or open-label phase (baseline to Visit 9/ET)

Laboratory	Double-blind	Placebo N=400	OTG N=389	Open-label	DB placebo N=107	DB OTG N=109
Hematocrit (N)		N = 372	N=367			
Low		13 (3.5%)	13 (3.5%)			
High		4 (1.1%)	7 (1.9%)			
Bilirubin		N= 375	N= 370		N=101	N=103
Low		0	0		0	0
High		1 (0.3%)	4 (1.1%)		1 (1%)	1 (1%)
AST*		N=374	N=369		N=100	N=103
Low		0	1 (0.3%)		0	0
High		24 (6.4%)	29 (7.9%)		11 (11%)	12 (11.7%)
ALT**		N=374	N=370		N=100	N=103
Low		3 (0.8%)	2 (0.5%)		0	0
High		33 (8.8%)	36 (9.7%)		8 (8.0%)	11 (10.7%)
GGT***		N=375	N=370		N=101	N=103
Low		1 (0.3%)	1 (0.3%)		0	0
High		21 (5.6%)	21 (5.7%)		4 (4.0%)	8 (7.8%)
Triglycerides		N=375	N=369		N=101	N=103
Low		0	0		0	0
High		26 (6.9%)	37 (10%)		8 (7.9%)	12 (11.7%)

* AST=aspartate aminotransferase
** ALT=alanine aminotransferase
** GGT=gamma-glutamyl-transferase

***Reviewer's comment**: It is unclear why there are a relatively high proportion of patients with abnormally high AST, ALT, and triglyceride in placebo and active groups. This will be a review issue.*

Outliers and dropouts for laboratory abnormalities: According to the sponsor, 46 patients (5.8%) had changes in laboratory parameters considered to be clinically significant that were reported as an adverse event, although none were considered as SAE.

***Reviewer's comment:** It is unclear what changes in laboratory parameters qualify as "clinically significant." A review of the summary of clinically significant changes in clinical laboratory parameters showed 7 events of LFT abnormalities (ALT increased, AST increased, GGT increased, liver function test abnormality, hepatic enzyme increased) in the placebo group compared to 23 events in the OTG group. It is unclear how many patients had these LFT abnormalities. These findings will be a review issue.*

***Reviewer's comment:** The sponsor should clarify what changes in laboratory parameters qualify as "clinically significant." The sponsor should also provide summaries of patients who had the following laboratory outliers:*

- AST ≥ 3X ULN and ≥ 5X ULN
- ALT ≥ 3X ULN and ≥ 5X ULN
- Total bilirubin ≥ 2X ULN
- Creatinine ≥ 2X ULN

Two patients randomized to OTG treatment had clinically significant liver enzyme elevations during the phase III study which led to study discontinuation.

- Patient 14505 had a history of benign liver mass and entered the study with elevated baseline liver enzymes (ALT, AST, GGT), which further increased after 12 weeks of OTG treatment during the double-blind period. The patient entered open-label treatment but was withdrawn from the study 12 days later due to elevations in liver enzymes. A follow-up evaluation 43 days following the final gel application showed ALT, AST and GGT to have decreased to levels that the investigator no longer felt to be clinically significant (see below). The total bilirubin levels were within normal limit (WNL) at all time points.

Patient 14505: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Follow-up (43 days after final dose)
ALT	2X	3X	1.9X
AST	1.1X	1.4X	WNL
GGT	1.4X	1.8X	WNL

- Patient 14520 had a history of hepatitis C infection and had elevated baseline ALT, AST and GGT, which also further increased after 12 weeks of OTG treatment in the double-blind period. The patient was in the open-label portion of the study for 1 day when the investigator requested the termination of the patient's participation. At a follow-up visit 21 days after the last OTG application, the ALT and AST levels had returned to normal and GGT level had fallen below baseline levels. The total bilirubin levels were WNL at all time points.

Patient 14520: Lab values expressed in terms of multiples of upper limit of normal (ULN)	Baseline	Week 12	Follow-up (21 days after final dose)
ALT	2X	4.3X	WNL
AST	2.2X	5.4X	WNL
GGT	2.8X	4X	2.1X

***Reviewer's comment**: Patients 14505 and 14520 had underlying liver disease prior to the start of the study, and the proposed label includes a general precaution on the use of OTG in patients with hepatic impairment. Liver test elevation is not a labeled safety issue with any of the approved oxybutynin products.*

Urinalysis: There were no differences in the proportion of subjects with abnormal urinalysis results between active and placebo treatment groups.

Clinical laboratory evaluations by sex, race, and age: According to the sponsor, no clinically relevant trends were noted for the clinical laboratory results based on age (< 65 years old versus ≥ 65 years old). The effects of gender and race on clinical laboratory parameters could not be assessed because of the very limited number of patients who were male and/or non-White.

3.5.4 Other Safety Evaluations

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], respiratory rate [RR], temperature [T]): No clinically relevant trends in mean values or in mean changes from baseline to endpoint were noted between placebo and active OTG groups or between patients treated < 12 weeks compared to those treated ≥ 12 weeks. In DB and OL phase III study analyzing for change from baseline to Endpoint vital signs, a total of 3 patients treated with OTG had vital sign values that met pre-defined clinically significant changes in vital signs (1

diastolic, 2 systolic) compared to 2 patients (1 diastolic, 1 pulse) in the placebo group. In the integrated phase 1 studies, one patient in the showering study (OG06006) met the pre-defined criteria for vital sign changes (diastolic). In the non-integrated studies, no clinically significant changes were observed.

Reviewer's comment: *A review of the summaries of vital signs by visit and treatment group for Study OG05009 showed no clinically significant differences in the mean or median SBP, DBP, or HR between different treatment groups.*

Reviewer's comment: *In Study OG05009, clinically significant changes were pre-defined as:*

- *SBP: Absolute change ≥ 20 mmHg AND endpoint SBP ≤ 90 mmHg or ≥ 180 mmHg*
- *DBP: Absolute change ≥ 15 mmHg AND endpoint DPB ≤ 50 mmHg or ≥ 105 mmHg*
- *HR: Absolute change ≥ 15 beats per minute (bpm) AND endpoint pulse ≤ 50 or ≥ 120 bpm.*

This reviewer recommends the following:

1. *Vital signs (blood pressure, pulse) for OAB patients should be summarized for baseline, each post-baseline visit, and change from baseline to each of these post-baseline visits in double blind and open-label phases of Study OG05009.*
2. *Summaries of clinically significant changes in vital signs for the absolute change from baseline (e.g., systolic BP change ≥ 20 mmHg) should be presented separately from those exceeding a pre-defined value (e.g. systolic BP ≥ 180 mmHg).*

Electrocardiograms (ECG's): ECG's were obtained at baseline and exit only during the DB phase III study. Overall, slightly higher proportion of placebo patients than OTG patients had ECG's that "worsened" from baseline (10% in OTG versus 13.1% in placebo). Nine ECG's (5 in OTG, 4 in placebo) were considered to be clinically significant.

Post-void residual volume: A PVR urine volume was measured via ultrasound or catheter immediately after voiding at screening and at completion of DB phase III study. Overall, the mean PVR urine volume remained unchanged following 12 weeks of treatment with OTG. Two patients with normal baseline values had PVR at endpoint > 250 mL (one patient each receiving OTG and placebo). An adverse event was reported for "increased post-void residual urine volume" for Patient 14145 receiving active treatment (Baseline (2/8/07) = (b) (4) mL, ET (2/26/07) = (b) (4) mL), but judged unrelated to treatment.

Reviewer's comment: *Patient 14145 permanently discontinued study medication 14 days after the first dose of study drug due to a 16-cm ovarian cystadenoma that required surgical intervention. Such a large ovarian cyst would have most likely been present at the start of the study only 14 days earlier, so it is not clear whether the elevated PVR volume at the end of treatment was related to the cyst or active OTG or some other factor. A review of the line listing of PVR measurements by each subject, however, did not indicate a trend of OTG use and elevated PVR.*

Person-to-person transference: The potential for dermal transfer of oxybutynin from a treated person to an untreated person was evaluated in Study OG06007. The untreated partners not protected by clothing had detectable plasma concentrations of oxybutynin (mean Cmax = 0.94 ng/mL). Twelve of the 14 untreated subjects whose partner covered the application site with clothing had no measurable blood levels of oxybutynin, while 2 untreated subjects showed trace levels (Cmax =0.1 ng/mL).

***Reviewer's comment**: Transference of oxybutynin to a partner via close contact can be adequately addressed in the product label.*

3.5.5 Preliminary safety and tolerability conclusions

- The safety profile of OTG 10% is similar to other anticholinergic products approved for the treatment of OAB and on its face, appears acceptable.
- Skin safety, especially skin sensitization, will be a review issue.
- Further assessments of laboratory and vital sign outliers will be conducted pending the sponsor's response to the information requested in the 74 Day letter.
- Compared to placebo, OTG treatment was not associated with an excess of serious adverse events, or hematologic or CNS or renal adverse events.
- Patient exposure to OTG is acceptable.
- No additional formal risk management program (RMP) activities are recommended at this time.

4 Other considerations of Filing Review

4.1 Review of Financial Disclosure Documents

Form FDA 3454 (4/06), dated January 18, 2008, and signed by Kevin Barber, Ph.D., Executive Director, Proprietary Regulatory Affairs, Watson Laboratories, was 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 will be 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 [21 CFR 54.2(a)], proprietary interest in the covered product or significant equity interest in the sponsor of the covered study product [21 CFR 54.2(b)], significant payments of other sorts from the sponsor of the covered study [21 CFR 54.2(f)]. There was no missing financial disclosure information for investigators of Study OG05009.

4.2 Labeling

The proposed label complies with the basic requirements of the Physician Labeling Rule (PLR). The content of the label is based on the findings of the clinical development of oxybutynin gel 10% and previously approved oxybutynin products. The proposed draft label included the following key clinically relevant sections:

(b) (4)

[redacted]

- CLINICAL STUDIES: Efficacy data in Study OG05009, including table of change from baseline urinary incontinence episodes, urinary frequency, and average volume per void and table of change from baseline in health outcome measures (IIQ and King's Health Questionnaire).

4.3 Consults

a. **Pediatric Review Committee (PeRC)**: The pediatric page should be forwarded to PeRC for review and comments.

Pediatric Waiver: The sponsor requested a waiver for conducting pediatric studies in children from birth through 4 years of age under 21 CFR 314.55(c)(2)(iii). This reviewer recommends granting this request pending evaluation by PeRC.

Pediatric Deferral: The sponsor requested a deferral for pediatric studies in children age 5 to 17 years old. The sponsor plans to first determine whether Oxytrol TDS is safe and effective in the pediatric population (Oxytrol Pediatric Study in pediatric patients with neurogenic bladder). If the results with Oxytrol are positive, the sponsor plans to discuss with the Division whether a pediatric study with OTG would be necessary. If the results of Oxytrol are negative, the sponsor may use these results to request a waiver for conducting pediatric studies in children age 5 to 17 years old.

If it is determined that a pediatric study of OTG is necessary and an acceptable protocol is developed, the sponsor intends to submit the final pediatric study report within 3 years after approval of OTG in the adult population.

Reviewer's comment: *During the EOP2 meeting held in August, 2005, the Division stated that that OTG would qualify for a pediatric waiver in children 0-4 years of age and a deferral of pediatric studies in other children. However, with the enactment of the FDAAA in 2007 and the creation of the Pediatric Review Committee (PeRC), these decisions will need to be re-evaluated with input from PeRC. The formulation of OTG (topical gel) appears to be age appropriate for all ages (assuming acceptable skin safety) making OTG a good candidate for drug development in the pediatric population.*

b. **Division of Scientific Investigations (DSI) Audit**: A limited, routine DSI audit of 2 or 3 large U.S. study sites is recommended, given that this is a new transdermal formulation and that Study OG05009 is the only confirmatory study supporting the safety and efficacy of OTG. This audit issue will be further discussed at the filing meeting.

c. **Office of Surveillance and Epidemiology (OSE):** to evaluate the 3 candidate trade names submitted electronically on April 25, 2008 (GELNIQUE™ (b) (4) [redacted] to review the drug label (Highlights and Full Prescribing Information), and to review the Patient Package Insert for content and label comprehension.

4.5 Other review disciplines

CLINICAL PHARMACOLOGY: Eleven clinical pharmacology studies were conducted during the development of OTG. A major objective of the clinical pharmacology development was to select a dose/formulation of OTG that would provide similar oxybutynin plasma concentrations as those provided by the Oxytrol TDS (3.9 mg/day) at steady state. The clinical pharmacology studies also evaluated the effects of different oxybutynin formulations, surface area of application, application site bioavailability, effects of showering and sunscreen application, and the potential for person-to-person transfer of oxybutynin.

CHEMISTRY, MANUFACTURING, AND CONTROL (CMC): The chemistry review team has identified no non-fileable issues.

PRECLINICAL TOXICOLOGY: Preclinical toxicology summary information is provided in Module 2 and the study reports are provided in Module 4 of the eCTD submission.

Non-clinical safety investigation was limited to an in vitro light absorption test to evaluate phototoxicity potential (Study ARD-RSR-0779), a dermal irritation study in rabbits (Study ONY00012) and a sensitization study in guinea pigs (Study ONY00013) to assess the local tolerance of the new topical gel product. Results of these studies did not indicate an adverse effect of OTG on the parameters evaluated.

5 Summary of Initial Clinical Review

Efficacy:

1. A preliminary review of the efficacy data appears to support efficacy of 10% OTG in the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency.
2. The changes from baseline in IIQ total score and subscales and in KHQ Domain Scores are considered exploratory endpoints. Currently the Division does not anticipate including data from these questionnaires in labeling.

Safety:

3. After a preliminary evaluation, the safety profile appears to be similar to other anticholinergic products approved for the treatment of OAB and on its face, appears acceptable.
4. Skin safety, especially skin sensitization, will be a review issue.
5. No additional formal risk management program (RMP) activities are anticipated at this time.

Others:

6. Review of the submitted financial disclosure did not reveal conflict of interest.
7. The format of the proposed label complies with the Physician Labeling Rule (PLR) and there are no clearly apparent deficiencies in the label.
8. Consults will be requested from the following: PeRC, DSI, and OSE.

Conclusion: From a clinical perspective, the NDA is fileable.

Addendum (May 14, 2008): An internal 45-day filing meeting was held with the various review disciplines. The discussions followed:

- The clinical, clinical pharmacology, biostatistics, chemistry and pharmacology/ toxicology teams all concluded that NDA 22-204 is fileable. Each review team had several comments to be conveyed to the sponsor, most of which involved information requests, in the 74 Day letter.
- After discussion with the representative from the Division of Scientific Investigations (DSI), the Division will request a routine DSI audit of two of the largest study sites (all in the U.S.) of Study OG05009.

Recommended Regulatory Action: The following **clinical** comments should be conveyed to the sponsor in the 74 Day letter.

1. Skin safety, especially skin sensitization, will be a review issue.
2. The changes from baseline in IIQ total score and subscales and in KHQ Domain Scores are considered exploratory endpoints. Currently the Division does not anticipate including data from these questionnaires in labeling.
3. Provide case narratives for all subjects/patients who discontinued prematurely due to an adverse event.
4. For Study OG05009, provide summaries for the following laboratory outliers:
   - AST $\geq$ 3X ULN and $\geq$ 5X ULN
   - ALT $\geq$ 3X ULN and $\geq$ 5X ULN
   - Total bilirubin $\geq$ 2X ULN
   - Creatinine $\geq$ 2X ULN
   - These summaries should be provided for placebo and OTG groups in the double-blind phase, and for treatment group with < 12 weeks OTG exposure and treatment group with $\geq$ 12 weeks of OTG exposure in the double-blind and open-label phases.
5. Define what changes in laboratory parameter are considered as "clinically significant" in Table 12-10 (page 88) of the Study Report for OG05009.
6. For Study OG05009, provide summaries of clinically significant changes in vital signs for the absolute change from baseline (e.g., systolic BP change $\geq$ 20 mmHg) separately from those exceeding a pre-defined value (e.g., systolic BP $\geq$ 180 mmHg).
7. We acknowledge your plans to fulfill the PREA requirements and will determine the acceptability of your proposed plans prior to the PDUFA date of January 27, 2009.

Christine P. Nguyen, M.D.
Medical Officer
Division of Reproductive and Urologic Products

Appendix A: GRMP Clinical Reviewer Filing Checklist

NDA Number: 22-204 **Applicant: Watson** **Stamp Date: 3/26/08**

Drug Name: To be determined **NDA Type: standard, original application**

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English, or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		An ISE was not necessary because there is only 1 phase 3 study (OG05009)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: KMD-3213-US021-99 Study Title: A Pilot, Phase II, Placebo-Controlled, Double-Blind Study of KMD-3213 in Patients with the Signs and Symptoms of Benign Prostatic Hyperplasia (BPH) Sample Size: 264 Arms: 3 Location in submission: Module 5 – 5.3.5.1	X			

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study#1: OG05009 Indication: OAB with urgency, frequency, and incontinence	X			
15.	Do all pivotal efficacy 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? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
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	13 of 14 studies, including the Phase III study, were conducted in the U.S.
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 arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	Thorough QT study was not necessary
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	There has been no marketing experience with OTG in any country.
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			The exposure is less than the ICH guidelines but is sufficient to assess safety and efficacy of OTG.
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			
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			
25.	Have narrative summaries been submitted for all deaths and		X		The sponsor has only

[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 as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				provided narratives for SAE's. Case narratives for dropouts due to non-SAEs will be requested in the 74 day letter.
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			The sponsor requests a partial waiver for pediatric studies in children from birth through 4 years of age and a deferral for pediatric studies in children age 5 years to 17 years.
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 efficacy 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			
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	X			

	Content Parameter	Yes	No	NA	Comment
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

[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.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74 Day letter.

1. Skin safety, especially skin sensitization, will be a review issue.
2. The changes from baseline in IIQ total score and subscales and in KHQ Domain Scores are considered exploratory endpoints. Currently the Division does not anticipate including data from these questionnaires in labeling.

Christine P. Nguyen

Reviewing Medical Officer Date

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/

Christine Nguyen
5/27/2008 10:01:13 AM
MEDICAL OFFICER

George Benson
5/27/2008 03:23:51 PM
MEDICAL OFFICER