CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-204**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**03/26/2008**
PRODUCT:	**Oxybutynin Transdermal Gel**
INTENDED CLINICAL POPULATION:	**men and women with overactive bladder**
SPONSOR:	**Watson**
DOCUMENTS REVIEWED:	**electronic**
REVIEW DIVISION:	**Division of Reproductive and Urologic Products (HFD-580)**
PHARM/TOX REVIEWER:	**Laurie McLeod-Flynn, Ph.D., D.A.B.T.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR:	**Scott Monroe, M.D.**
PROJECT MANAGER:	**Celia Peacock, MPH, RD**

Date of review submission to Division File System (DFS): 26 November 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There is no impediment to approval from a Pharmacology/Toxicology perspective

B. Recommendation for nonclinical studies: None are recommended at this time.

C. Recommendations on labeling:

8 PREGNANCY

8.1 Pregnancy Category B

There are no adequate and well-controlled studies of topical or oral oxybutynin use in pregnant women. (b) (4)

Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride.

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum exposure in humans taking an oral dose, based on body surface area. Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems. Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The pharmacology and toxicology of oxybutynin have been well-characterized in numerous *in vitro* and *in vivo* studies. The excipients of the final formulation are either United States Pharmacopeia (USP), National Formulary (NF), or supported by respective Drug Master Files (DMF). The safety of transdermally administered oxybutynin has been well-established with Oxytrol. Because oxybutynin has been extensively studied,

nonclinical investigations of Oxybutynin Transdermal Gel were limited to in vitro human cadaver skin permeation studies to estimate a delivered dose, a primary skin irritation study in rabbits (Study ONY00012), a sensitization study in guinea pigs (Study ONY00013), and a light absorption test (ARD-RSR-0779) to evaluate phototoxicity potential. The battery of nonclinical studies did not demonstrate OTG to be irritating or sensitizing, and no significant absorbance of simulated sunlight was observed that would indicate a phototoxic potential. Clinical skin irritation and sensitization studies were also conducted.

B. Pharmacologic activity: Oxybutynin is an antispasmodic /anticholinergic.

C. Nonclinical safety issues relevant to clinical use

There are no unresolved issues. The active ingredient in this product, oxybutynin chloride, has been in clinical use for over 30 years. The sponsor reports that no unexplained toxicity or exaggerated pharmacology has been observed clinically.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22204
Review number: 1
Sequence number/date/type of submission: 000 / 27 March 2008 / original submission
Information to sponsor: Yes ( ) No (x)
Sponsor and/or agent: Watson

Reviewer name: Laurie McLeod-Flynn
Division name: Division of Reproductive and Urologic Products
HFD #: 580
Review completion date: 25 November 2008

Drug:

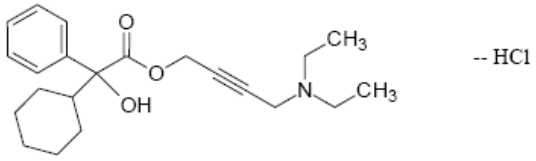
Trade name: Oxybutynin Chloride Topical Gel

Chemical name: 4-diethylamino-2-butynyl-(±)-α-cyclohexyl-α-phenylglycolate hydrochloride

CAS registry number: 5633-20-5

Molecular formula/molecular weight: $C_{22}H_{31}NO_3$ / 357.5

Structure:



Relevant INDs/NDAs/DMFs: IND 67126,

Drug class: antispasmodic, anticholinergic

Intended clinical population: men and women with overactive bladder

Clinical formulation:

Material	% weight	grams
Oxybutynin Chloride, USP	10.0	0.100
Purified Water, USP	(b) (4)	
Alcohol, USP		
Glycerin, USP		
Sodium Hydroxide, 2N (Sodium Hydroxide, NF and Purified Water, USP)		
Hydroxypropyl Cellulose, NF		
Total	100%	1.00 g

Route of administration: dermal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

[For (b)(2) applications:

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22204 are owned by Watson or are data for which Watson has obtained a written right of reference. Any information or data necessary for approval of 22204 that Watson does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Watson does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22204.

2.6.2 PHARMACOLOGY

From the Oxytrol label:

Oxybutynin acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors, resulting in relaxation of bladder smooth muscle. In patients with conditions characterized by involuntary detrusor contractions, cystometric studies have demonstrated that oxybutynin increases maximum urinary bladder capacity and increases the volume to first detrusor contraction.

Oxybutynin is a racemic (50:50) mixture of R- and S- isomers. Antimuscarinic activity resides predominantly with the R-isomer. The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in *in-vitro* studies.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Oxybutynin pharmacokinetics and metabolism have been extensively studied clinically.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

Oxybutynin chloride has been in clinical use for over 30 years. The sponsor reports that no unexplained toxicity or exaggerated pharmacology has been observed clinically.

Genetic toxicology:

Oxybutynin was negative for genotoxicity in bacterial reversion assays, a chromosomal aberration test using mammalian cells (fibroblast derived from Chinese guinea pig lung) and a mouse micronucleus test.

From the Oxytrol label: Oxybutynin chloride showed no increase of mutagenic activity when tested in *Schizosaccharomyces pompholiciformis, Saccharomyces cerevisiae*, and *Salmonella typhimurium* test systems.

Carcinogenicity:

The potential carcinogenicity of oxybutynin was not investigated by the sponsor. No relevant publications in the scientific literature were found. The product labeling reflects the historical carcinogenicity labeling for oxybutynin products.

From the Oxytrol label: A 24-month study in rats at dosages of oxybutynin chloride of 20, 80 and 160 mg/kg showed no evidence of carcinogenicity. These doses are approximately 6, 25 and 50 times the maximum exposure in humans taking an oral dose based on body surface area.

Reproductive toxicology:

Oxybutynin was administered subcutaneously at dose rates of 0, 5, 25 or 125 mg/kg/day to Sprague-Dawley rats of both sexes. In males, oxybutynin was given for 4 weeks prior to mating. Oxybutynin induced a decreased count of luteal bodies in the 25 mg/kg/day group. The number of implantations and live embryos were consequently decreased but there was no statistically significant change in the number of implantations or on the embryo mortality. A dose of 5 mg/kg caused mydriasis but was otherwise without toxic effect in this test.

A series of reproductive toxicity studies have been reported in the literature by Edwards et al. These studies examined oxybutynin given by oral gavage for its effect on fertility

and peri- and post-natal development in the rat and its embryotoxic potential in the rat and rabbit. In the fertility study, groups of 24 male and female rats each received doses of 0, 3, 15 or 75 mg/kg/day oxybutynin by oral gavage, from 9 weeks prior to mating for males and 2 weeks prior to mating for females. No treatment related effects on mating or pregnancy rate were observed.

Oxybutynin was administered subcutaneously to female rats at doses of 0, 1, 5, or 25 mg/kg/day given on days 7-17 of pregnancy. There were no treatment related effects on the maintenance of pregnancy or on embryo /fetal development at any dose.

Oxybutynin was administered subcutaneously to female rabbits at doses of 0, 0.2, 0.3, 0.4 mg/kg/day on days 6-18 of pregnancy). There were no treatment related effects on pregnancy or on embryo/fetal development up to 0.3 mg/kg. At 0.4 mg/kg there was an increase in unspecified organ abnormalities, although no other toxicities were observed.

Edwards et al. examined the effects of oxybutynin on embryo/fetal development in rats and rabbits. Groups of 36 female Sprague-Dawley rats received doses of 0, 4, 20 or 100mg/kg/day oxybutynin by oral gavage. Reproductive performance was affected at 100 mg/kg/day; there was an increase in malformation incidence and mean duration of gestation was extended. There were no clear effects on development at 4 or 20 mg/kg/day.

Groups of 16 female New Zealand white rabbits received doses of 0, 3, 12 or 48 mg/kg/day oxybutynin by oral gavage. No increased incidences of skeletal or visceral anomalies were observed.

Edwards et al. also examined peri-natal effects and post-natal development of oxybutynin. Groups of 24 female Sprague-Dawley rats received doses of 0, 4, 20 or 50 mg/kg/day oxybutynin by oral gavage from Day 17 of gestation to Day 21 postpartum. No evidence of dystocia or extended gestation period was observed. Pup mortality was slightly increased and pup weight gain was reduced at 50 mg/kg/day (the highest dose tested) but 4 and 20 mg/kg/day had no significant effects on the parameters studied.

From the Oxytrol label: Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility or harm to the animal fetus. Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride. The safety of OXYTROL administration to women who are or who may become pregnant has not been established. Therefore, OXYTROL should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

Reproduction studies with oxybutynin chloride in the mouse, rat, hamster, and rabbit showed no definite evidence of impaired fertility.

Special toxicology:

Primary Skin Irritation Study in Rabbits (Study ONYOOOI2) A 10% w/w OTG formulation, identical in composition to the intended commercial formulation, was tested for skin irritation potential in rabbits. Each of six New Zealand White rabbits (6M, 6F) received the treatments of active and placebo gel to shaved intact skin sites. Each site was exposed to the test article and then covered with a 1" by 1" gauze square for 23 hours and the treatment repeated daily for 5 days. Skin irritation was assessed 1 hour after removal of the gauze square on Days 1, 2, 3, and 4 and at 1, 24, 48, and 72 hours after final test article removal on Day 5. Dermal response was scored using the Macroscopic Dermal Grading System. An overall score of ~ 4.99 is regarded as a nonirritant. The study was conducted in accordance with Good Laboratory Practices (GLP). Based on the average for all observations, the primary dermal irritation index was calculated as 0.50 (non-irritant) for the placebo gel and 2.08 (non-irritant) for the active oxybutynin gel, both scores based on erythema reaction. The active test article resulted in very slight to well-defined erythema being noted on 6/6 test sites during the Day 1 scoring interval. Very slight to slight edema was noted on 5 of 6 test sites on Day 4 scoring interval. The dermal irritation resolved completely on 2 of 6 sites by 72 hours and on the remaining sites by the Day 7 scoring interval.

Sensitization Study in Guinea Pigs (Study ONYOOOI3) A 10% w/w OTG formulation, identical in composition to the intended commercial formulation, was tested for sensitization potential in guinea pigs. Each of the test groups of 10 (5 male, 5 female) Hartley-derived albino guinea pigs received one treatment per week for three consecutive weeks of either test article (active or placebo gel). Following a 2-week rest period, a challenge was performed whereby the two test groups and two challenge control groups (five previously untreated, naïve, animals for each test article) were topically treated with the appropriate test article. Challenge responses in the test animals were compared with those of the appropriate challenge control animals. Application was accomplished by placing 0.3 ml of the test article in a 25 mm Hiltop chamber. The loaded chambers were then applied to the clipped surface of the animal (once a week for 3 weeks). After 6 hours of exposure the chambers were removed and the test sites were wiped with moistened gauze. At 24 and 48 hours following each application, the skin was scored for erythema and edema using the Draize scoring method. The challenge phase was conducted 14 days after the last induction dose was applied. The challenge treatment was applied for 6 hours and the skin was assessed for irritation at 24 and 48 hours following chamber removal. The study was conducted in accordance with GLP. The response to a-hexyIcinnamaldehyde (a known dermal sensitizer) was based on historical control data generated at the testing facility. At the time of the challenge exposure, none of the placebo-treated animals exhibited dermal responses either 24 or 48 hours post-application, while 6 of 20 animals in the historical challenge control group exhibited an erythema score of 1 at 24 and 48 hours. The animals in the active treatment demonstrated the same results as the placebo animals, i.e. none had a dermal response to the test article

at 24 and 48 hour observations. Neither the active nor placebo gel produced delayed contact sensitization.

Light Absorption Experiment (ARD-RSR-0779) The final OTG formulation and a placebo control, the final formulation excluding the active pharmaceutical ingredient, were used in the study to evaluate the phototoxicity potential of the gels (b) (4) Absorbance through remaining wavelength spectrum of concern was insignificant. Significant absorption at the wavelengths of interest was not observed. Therefore, phototoxicity is not expected to occur.

Toxicity review of impurities:

Leachable studies were conducted for OTG with the (b) (4) pouching materials to identify whether any leachables from the pouching materials were present in the drug product. The leachable studies identified four chemicals from the (b) (4) pouch materials: (b) (4) All of these leachables are present in the food industry as food additives or indirect food additives and have been studied in repeat dose, genotoxicity, and reproductive and developmental toxicology studies available in the literature. In addition, the three leachables (b) (4) are present in the approved Androgel 1% drug product at amounts that are comparable with those found in the OTG drug product.

Maximum Daily Topical Exposure of Leachables

Leachable	Pouching material	Maximum topical exposure amount/day (µg/day)
(b) (4)		

(b) (4)

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(b)(4) CCI/TS

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There is no impediment to approval from a Pharmacology/Toxicology perspective.

Unresolved toxicology issues (if any): There are no unresolved toxicology issues.

Recommendations: Approval is recommended.

Suggested labeling: See executive summary.

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/s/

Laurie McLeod
11/26/2008 12:43:44 PM
PHARMACOLOGIST

Lynnda Reid
11/26/2008 12:49:46 PM
PHARMACOLOGIST
I concur 1) that nonclinical data support approval, and
2) with the proposed labeling recommendations.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22204 **Applicant: Watson Labs** **Stamp Date: 27 March 2008**

Drug Name: Oxybutynin chloride topical gel **NDAType: 505 b1**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/ toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		

	Content Parameter	Yes	No	NA Comment
7	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?			NA
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)		X	Reviewable toxicology data for the four leachable substances found in the drug product should be provided, justifying their safe use under chronic dermal exposure conditions. Structure activity analysis for the metabolite PCGA and the two (b) (4) impurities should be provided for review.
11	Has the sponsor addressed any abuse potential issues in the submission?			NA
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments:

Articles from publicly available literature and references to previously approved forms of Oxybutynin were submitted. The proposed label is consistent with the label of previously approved products.

Two (b) (4) impurities have been reported which are below the qualification limit, but for which structure activity analyses should be provided.

In-Vitro Biological Reactivity, and Extractables/Leachables studies were performed on the pouch material. Toxicity evaluations were provided for 4 detectable leachables: [redacted] (b) (4). Reviewable toxicology data for the four leachable substances found in the drug product should be provided, justifying their safe use under chronic dermal exposure conditions.

Structure activity analysis for the metabolite PCGA should be provided for review.

Reviewing Pharmacologist	Date
Team Leader/Supervisor	Date

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/s/

Laurie McLeod
6/10/2008 12:34:20 PM
PHARMACOLOGIST

Lynnda Reid
6/10/2008 12:36:01 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-204 / N000
Drug Name:	Oxybutynin Chloride Topical Gel, 100 mg, Topical Gel Formulation
Indication(s):	Overactive bladder with symptoms of urge urinary incontinence, urgency and frequency
Applicant:	Watson Laboratories, Inc
Date(s):	Submitted 03/26/2008 PDUFA: 01/27/2009
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Xin Fang, Ph.D. , Statistical Reviewer
Concurring Reviewers:	Sonia Castillo, Ph.D. , Acting Team Leader
Medical Division:	Division of Reproductive and Urological Drug Products
Clinical Team:	Christine Nguyen, M.D., Medical Reviewer Suresh Kaul, M.D., Team Leader
Project Manager:	Jennie Roule

Keywords: NDA review, Clinical studies, ANCOVA, Multi-center

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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

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

1.2 Brief Overview of Clinical Studies

The applicant, Watson Laboratories, reported efficacy and safety data from one Phase 3 clinical trial (Study OG05009) to support the use of Oxybutynin Topical Gel (OTG) in the treatment of overactive bladder symptoms (OAB). Study OG05009 was a multi-center, double-blind, placebo-controlled, 12-week study of the efficacy and safety of daily dosing with OTG to treat the symptoms of overactive bladder followed by a 14-week open-label safety extension.

The protocol-specified primary efficacy endpoint was the change from baseline (CFB) to endpoint (Week 12) in the number of urinary incontinence episodes per day. The secondary endpoints included average daily urinary frequency, nocturia (nighttime urinary frequency), urine volume per void, IIQ domain scores and total score, KHQ domain scores and achievement of continence.

The primary objective of this study is to demonstrate the efficacy of a 1 g dose of 10% OTG in the treatment of OAB. The secondary objectives included evaluation of additional efficacy measures and population pharmacokinetics of the product. The objective of the open-label safety extension was to demonstrate continued systemic and dermatologic safety of 10% OTG in patients with OAB.

1.3 Statistical Issues and Findings

There were no issues with regards to study conduct or statistical analysis of the primary efficacy endpoint. There were uncertainties about the drug's effect on urinary frequency in male patients and on urine void volume in non-Caucasian patients. The analysis results for these and other subgroups were inconclusive because of decreased power due to small sample size.

2. INTRODUCTION

2.1 Overview

The applicant (Watson Laboratories, Inc.) is seeking approval of 1 g 10% OTG for the treatment of OAB with symptoms of urgency, urge urinary incontinence, and urinary frequency [redacted] (b) (4)

Oxytrol® Oxybutynin Transdermal System 3.9 mg/day was developed by the applicant and was approved by FDA in 2003. Although the transdermal system proved to be safe and effective in clinical trials, some bothersome side effects were commonly reported at application sites, including pruritus and erythema. The applicant developed a once-a-day topical gel system with improved skin tolerability. Both transdermal deliver systems have the same active ingredient, oxybutynin. The pharmacokinetics of both systems was comparable.

To support the safety and efficacy of OTG, clinical data from one Phase 3 study was submitted. The protocol was titled "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". The study's double-blind period is summarized in Table 2.1.

Table 2.1 Summary of Study OG05009

Study Site (number)	Study Design	Number Randomized/ Study Regimen	Duration of Treatment
76 US sites	Two arms: placebo arm and OTG arm	Target size: 700 Total Screened: 1916 Total Randomized: 789 Placebo: 400 OTG: 389	12 weeks

Source: Statistical reviewer's listing.

2.2 Data Sources

The study report and additional information for this study were submitted electronically. The submitted SAS data sets for the study were complete and well documented. Analysis datasets were received on March 27, 2008 and located at

\\CDSESUB1\EVSPROD\NDA022204\0000\m5\datasets\og05009\analysis

and the data definition file was located at

\\CDSESUB1\EVSPROD\NDA022204\0000\m5\datasets\og05009\analysis\define-analysis.pdf.

2.3 Indication

Oxytrol® Oxybutynin Transdermal System (OTG) is indicated for the treatment of overactive bladder with symptoms of urgency, urge continence, and urinary frequency.

3. STATISTICAL EVALUATION

3.1 Overview of Study OG05009

3.1.1 Study Design

Study OG05009 was a multi-center, double-blind, placebo-controlled, parallel-group, 12-week study conducted at 76 US sites submitted by the applicant to support the use of once daily OTG in the treatment of overactive bladder symptoms (OAB). The double-blind period was followed by a 14-week open-label safety extension. The 76 US sites randomized 789 healthy OAB patients, who had a

history of urgency, urge urinary incontinence and urinary frequency, to receive either OTG or placebo. During the double-blind treatment period, efficacy and safety data were collected at weeks 1, 4, 8 and 12. Out of 789 randomized patients, 216 patients were enrolled into the open-label period for safety evaluation.

The primary study objective was to demonstrate the efficacy of a 1 g dose of 10% OTG compared to placebo gel in the treatment of OAB. The secondary objectives included evaluation of additional efficacy measures and population pharmacokinetics of the product. The objective of the open-label safety extension was to demonstrate continued systemic and dermatologic safety of 10% OTG in patients with OAB.

The protocol-specified primary efficacy endpoint was the change from baseline (CFB) to endpoint (Week 12) in the number of urinary incontinence episodes per day. The average number of episodes per day was calculated by dividing the total number of episodes (leakage due to either urge or stress) recorded on the 3-day urinary diary by the number of days with data recorded in the diary as follows:

Urinary Incontinence = Sum (Day 1+ Day 2 + Day 3 Episodes) / Number of Days in Diary

The protocol-specified secondary endpoints were defined as the CFB to Endpoint (Week 12) for the following parameters:

- The average daily urinary frequency was calculated by dividing the total number of incontinence episodes and normal voids recorded on the 3-day urinary diary by the number of days with data recorded in the diary as follows:
  Frequency = Sum (Day 1+ Day 2 + Day 3 Events) / Number of Days in Diary
- The average urine volume per void was only collected on 2 of the 3 days in the diary and was calculated as the average of the urine volumes recorded in the diary as follows:
  Urine volume per void = Sum (of Day 2 + Day3 Volumes)/ Number of volumes
  However, if the patient recorded volumes for all 3 days, only the first 2 days' data were used in calculating the parameter.
- Average nocturia (nighttime urinary frequency) were calculated by dividing the total number of events, defined as normal voids or episodes occurring after bedtime recorded on the diary by the number of days with data recorded in the diary.
  Nocturia = Sum (of Day 1+ Day 2 + Day 3 Events after bedtime)/ Number of Days in Diary
- Incontinence Impact Questionnaire (IIQ) domain scores and total score
- King's Health Questionnaire (KHQ) domain scores
- Achievement of continence.

For the secondary endpoints, no adjustment for multiplicity was pre-specified in the protocol. Of these secondary endpoints, the average daily urinary frequency and average urine volume per void are considered to provide additional supportive clinical evidence for the primary efficacy endpoint of the average daily number of urinary incontinence episodes. In addition, there is no further reporting of the nocturia, IIQ, KHQ, and achievement of continence endpoints as these quality-of-life endpoints have not been validated for this patient population.

For comparing the CFB between the OTG and placebo treatment groups, an ANCOVA model with baseline number of urinary incontinence episodes per day as covariate and treatment and center as fixed effects was used and tested at the 2-sided 0.05 significance level. The treatment-by-baseline interaction was examined at the 0.05 significance level using the Type III F-statistic corresponding to

the interaction effect. In addition, the treatment-by-center interaction was explored at the 0.10 significance level. In the event that the data normality assumptions were not met, an RT-2 rank transformation (rank data within center) was applied to the data. Missing data was imputed by LOCF, which was the primary method to account for missing data.

Small study centers, defined as those with fewer than 3 patients for any treatment group, were pooled. Within the group of small centers, pooling was performed from the largest to the smallest with respect to the total number of patients, and then by center number within those having the same size. Study centers were pooled until the pooled center had at least 3 patients in each treatment group. Any leftover centers from this procedure that do not have a sufficient number of patients to form a pooled center were pooled with the last pooled center. If at least 10% of the centers were pooled, the ANCOVA models did not included center.

Three patient populations were used in the analysis of efficacy and are listed in Table 3.1. The modified intent-to-treat (mITT) population was defined as the primary analysis population and included all randomized subjects who had received at least one dose of study drug and provided baseline efficacy assessment under actual treatment. The intent-to-treat (ITT) population was defined as secondary analysis population and was the same as the mITT except that the randomized treatment was used for treatment. The evaluable population was defined as a secondary analysis population and included all patients in the mITT population who were without significant protocol violations and completed 12 weeks of treatment. All efficacy and subgroup analyses were performed on mITT population. All secondary populations were used to perform sensitivity analyses to examine the effect of missing data on the efficacy analyses.

Table 3.1 Number of randomized subjects in each population

Regimen (parallel group)	Planned to Enroll (N=700)	Randomized (N=789)	MITT* (N=789)	ITT (N=789)	Evaluable (N=663)	Safety (N=663)
1 g 10% OTG	350	391	389	391	325	389
Placebo	350	398	400	398	338	400

Source: Table 14.1-1 of the study report
* MITT: modified intent-to-treat

The ITT population is essentially the same as the mITT population, except that four patients (13218, 14121, 16517, and 17214) received placebo (coded as placebo in the mITT population) when they should have received active treatment (coded as active treatment in ITT population), and two patients (16518 and 17205) received active treatment (coded as active treatment in the mITT population) when they should have received placebo (coded as placebo in the ITT population).

Sensitivity analyses were done to examine the effects of missing data on the LOCF efficacy analyses for urinary incontinence episodes, average daily urinary frequency, nocturia, and urine volume per void. The methods consisted of observed case analysis; baseline carried forward analysis; regression model imputation for missing data; and a repeated measure, mixed model ANCOVA with fixed effects of treatment, time, treatment-by-time interaction, and baseline values using different covariance structures.

The sample size was calculated using two sided t-test to detect a statistically significant (α=0.05) difference between OTG and placebo treatments for CFB in the number of urinary incontinence

episodes per day at Week 12. The standard deviation for the episodes per day was assumed at 2.25. The assumed difference for CFB between OTG and placebo was -0.52. The sample size per treatment arm for 80%, 85% and 90% of power was found to be 295, 350 and 395, respectively. The targeted enrollment was 350 patients per arm, for a total of 700 patients. For the additional 14-week safety extension evaluation, it was decided to enroll 200 patients from double-blind treatment in order to have at least 50 patients exposed to OTG for 6 months.

3.1.2 Reviewer's Comments on the design

The sample size was adequate for testing the superiority hypothesis for the CFB in the number of urinary incontinence episodes per day at Week 12/LOCF. Baseline comparability was examined through the treatment-by-baseline effect, which was appropriate.

3.2 Results

3.2.1 Patient Disposition, Demographic and Baseline Characteristics

Table 3.2 shows the comparability about patient characteristics between placebo and OTG treatments. Out of 701 completers (346 in OTG, 355 in Placebo), 216 patients (109 in OTG, 107 in Placebo) were randomized into the open-label extension period in the same study for a long-term safety evaluation. A total of 86 patients were exposed to OTG treatment for 26 weeks.

Table 3.2 Disposition of Subjects: Study OG05009

Subjects	Treatment groups	
	Placebo QD dose	1 g of 10% OTG QD
Total screened	1916	
Total randomized	400	389
Completed study	355	346
Discontinued (%):		
• Adverse event	13(3.3)	19(4.9)
• Lack of efficacy	3(0.8)	2(0.3)
• Withdrawn consent	17(4.3)	13(3.3)
• Protocol deviation	3(0.8)	1(0.3)
• Compliance	1(0.3)	0(0.0)
• Lost to follow-up	8(2.0)	9(2.3)
• Concomitant medicine	1(0.3)	0(0.0)
• Other reasons	2(0.5)	1(0.3)
Demographics:		
• Race	White: 335; Asian: 7 Black or African American: 54 American Indian/Alaska Native: 1 Multiracial: 3	White: 346; Asian: 6 Black or African American: 33 American Indian/Alaska Native: 2 Multiracial: 2
• Age	< 65 years: 260; >= 65 years: 140	< 65 years: 246; >= 65 years: 143
• Gender	Male: 48; Female: 352	Male: 37; Female: 352
• BMI	Missing: 3 < 32 kg/m^2: 226; >= 32 kg/m^2:171	< 32 kg/m^2: 230; >= 32 kg/m^2:159
Full analysis population (ITT-LOCF)	398	391
Full modified analysis population (mITT-LOCF)	400	389
Evaluable population	338	325

Source: Tables 14.1-1, 14.1-2, and 14.1-4 of the study report and statistical reviewer's analyses.

3.2.2. Primary Efficacy

For comparison of efficacy between the OTG and placebo treatments, the sponsor used an ANCOVA model on the normalized RT-2 transformed data (rank within center and divided the rank by center size plus 1). The sponsor first decided not to pool centers and dropped the effect of center in the ANCOVA model. We agree with this since the number of centers with fewer than 3 patients per treatment is 26 (34%), which adheres to the protocol. The model included baseline covariate, effect of treatment and baseline-by-treatment interaction if the interaction effect was statistically significant at α=0.05. Otherwise, the model included baseline and effect of treatment only. The use of normalized RT-2 transformation was motivated by two scenarios, which we do not agree in general. The first was to have a more robust test under normality violation. The second was to minimize the effect of center size. Note that the effect size for center may be increased due to more greatly reduced variance. Also, the treatment effect size may increase for the same reason. Although the RT-2 transformation itself was robust in terms of distribution, the transformed data did not satisfy the normality assumption either. We performed a non-parametric test (Wilcoxon Rank Sum) to confirm the corresponding efficacy result, in which the rank was taken across the center to be consistent with a parametric test. The sponsor examined the normality assumption of the untransformed data for skewness and kurtosis using the method of D'Agostino et al (1990), which pools the residuals from both treatment groups. In addition, the sponsor examined the homogeneity of variances across treatment groups using Levene's Test (Glaser, 1982). We performed an alternative analysis allowing unequal variances across treatment groups of the untransformed data to further confirm the efficacy results.

The primary efficacy endpoint in this study was the change from baseline (CFB) in number of urinary incontinence episodes per day to endpoint (Week 12/LOCF). The sponsor and reviewer results are presented in Table 3.3. Use of OTG resulted in a decrease of 0.5 urinary incontinence episodes per day compared to placebo ($p<0.01$). Results performed on the ITT population were consistent with those from the mITT population.

Table 3.3
Change from baseline to Week 12 in the mean number of daily urinary incontinence episodes for the mITT-LOCF population

	Treatment group (N)	Baseline Mean	CFB (LS Mean)	Treatment different	P-values without transformation		P-values with transformation	
					Equal variance	Unequal variance	RT-2 rank	Wilcoxon rank sum
Number of urinary incontinence episodes per day	Placebo (400)	5.4	-2.5					
	1 g of 10% OTG (389)	5.4	-3.0	-0.5	0.0062	0.0062	<.0001	<.0001

Source: Appendix 16.1.9.2.1 of the study report except the shaded data from statistical reviewer's analyses.

3.2.3 Secondary Efficacy

The secondary efficacy endpoints of clinical interest are the CFB to Endpoint (LOCF) in mean daily urinary frequency and mean urine volume per void. The sponsor performed analyses similar to those for the primary endpoint. Although p-values are presented, they should not be interpreted in the strict

sense of success for these secondary efficacy endpoints because no adjustment for multiplicity was pre-specified in the protocol. The sponsor and reviewer results are presented in Tables 3.4 and 3.5.

Change in Mean Daily Urinary Frequency:

As shown in Table 3.4, the mean daily urinary frequency was numerically decreased by 0.5 when using OTG compared to placebo.

Table 3.4
Change from baseline to Week 12 in the mean daily urinary frequency on mITT-LOCF population

	Treatment groups (N)	Baseline Mean	CFB (LS Mean)	Treatment different	P-values without transformation		P-values with transformation	
					Equal variance	Unequal variance	RT-2 rank	Wilcoxon rank sum
Number of daily urinary frequency	Placebo (400)	12.2	-2.0					
	1 g of 10% OTG (389)	12.4	-2.7	-0.5	0.0054	0.0055	0.0017	0.0022

Source: Appendix 16.1.9.3.1 of the study report except the shaded data from statistical reviewer's analyses.

Change in Average Urine Volume per Void:

Table 3.5 shows that the mean urinary volume per void was numerically increased by 16.2 ml when using OTG compared to placebo.

Table 3.5
Change from baseline to Week 12 in the mean urinary volume per void on mITT-LOCF population

	Treatment groups (N)	Baseline Mean	CFB (LS Mean)	Treatment different (ml)	P-values without transformation		P-values with transformation	
					Equal variance	Unequal variance	RT-2 rank	Wilcoxon rank sum
Number of daily urinary volume	Placebo (400)	167.9	3.8					
	1 g of 10% OTG (389)	163.4	21.0	16.2	0.0001	0.0001	0.0018	0.0002

Source: Appendix 16.1.9.5.1 of the study report except the shaded data from statistical reviewer's analyses.

3.2.4 Reviewer's comments on the efficacy results

Results from our alternative analyses confirmed the sponsor's findings on efficacy for 1 g of 10% OTG QD treatment for 12 week compared to placebo, and resulted in a statistically significant reduction in daily urinary continence episodes. Descriptively, there is a numerical reduction in daily urinary frequency and a numerical increase in the urinary volume per void at Week 12. We do not recommend reporting p-values for secondary endpoints because the study was not designed with adequate power to demonstrate efficacy with regard to the secondary endpoints.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Four subgroup populations were analyzed: gender, race, geriatric status and body mass index (BMI).

4.1 Gender, Race and Age

Gender, race and age are categorical variables with values of male and female for gender, Caucasian and non-Caucasian for race and <65 and ≥65 years for age. The sponsor performed subgroup analyses with the same ANCOVA model used for the primary efficacy analysis for each category of each subgroup for the mITT population. Descriptive statistics and the ANCOVA results are presented in Table 4.1. Although p-values are presented, they should not be interpreted in the strict sense because there was lack of power and no pre-specified adjustment for multiplicity in the protocol.

Table 4.1
CFB at Week 12 (LOCF) for number of daily urinary incontinence episodes in subgroup analyses

	Descriptive statistics			Results from ANCOVA model			
	Value (N)	Mean (SD)		LS Mean (SE)		P-value	
		Placebo	Active	Placebo	Active	Without Transform	RT-2 Transform
Gender	Female (704)	-2.49 (3.05)	-2.98 (2.77)	-2.47 (0.1388)	-3.00 (0.1388)	0.0074	<0.0001
	Male (85)	-2.35 (3.17)	-2.94 (2.37)	-2.42 (0.3816)	-2.85 (0.4348)	0.4587	0.3815
Race	Caucasian (681)	-2.49 (2.86)	-3.00 (2.69)	-2.49 (0.1362)	-2.99 (0.1340)	0.0100	0.0003
	Non-Caucasian (108)	-2.34 (3.96)	-2.91 (3.09)	-2.40 (0.4018)	-2.83 (0.4941)	0.5013	0.2458
Age	< 65 years (506)	-2.60 (3.30)	-3.18 (2.76)	-2.62 (0.1675)	-3.16 (0.1722)	0.0237	0.0003
	≥ 65 years (283)	-2.23 (2.56)	-2.63 (2.67)	-2.21 (0.2054)	-2.65 (0.2032)	0.1273	0.1085
BMI	< 32 kg/m^2 (456)	-2.46 (3.01)	-2.93 (2.70)	-2.47 (0.1608)	-2.92 (0.1594)	0.0473	0.0025
	≥ 32 kg/m^2 (330)	-2.52 (3.11)	-3.05 (2.80)	-2.53 (0.2136)	-3.05 (0.2215)	0.0909	0.0246

Source: Appendices 16.1.9.2.4 through 16.1.9.2.7 of the study report.

For gender, 10.8% (85/789) of the patients were male. The estimated reductions in daily urinary incontinence episodes are -0.53 episodes in females and -0.43 episodes in males. We performed an alternative ANCOVA analysis on all data (female and male) with baseline value nested within gender in the model and effect of treatment, gender and treatment-by-gender interaction using the untransformed data and RT-2 transformed data. Results of this analysis do not support a gender effect in the reduction of daily urinary incontinence episodes. In all, both the sponsor's and our analyses do not provide evidence for a gender effect in the reduction of daily urinary incontinence episodes. For urinary frequency in males, instead of showing a decrease, the number of daily urinary frequency increased by 0.52 episodes for OTG compared to placebo (Table 4.2). Given the small sample size, this result is not meaningful.

For race, 13.7% (108/789) were non-Caucasian. The estimated reduction in daily urinary incontinence episodes is 0.49 in Caucasians and 0.43 in non-Caucasians. Both the sponsor's and our analyses do not

provide evidence for a race effect in the reduction of daily urinary incontinence episodes. For urine void volume in non-Caucasians, instead of showing an increase, the urine volume void decreased by 12.5 ml for OTG compared to placebo (Table 4.3). Given the small sample size, this result is not meaningful.

For age, 35.9% (283/789) of patients were 65 years of age or older. The estimated reduction in daily urinary incontinence episodes is 0.55 in patients younger than 65 years of age and 0.44 in patients 65 years of age or older. Both the sponsor's and our analyses do not provide evidence for a geriatric effect in the reduction of daily urinary incontinence episodes, the reduction in urinary frequency, and the increase in urine void volume (Tables 4.2 and 4.3).

4.2 Other Special/Subgroup Population

Body Mass Index (BMI) was a variable with values of < 32 kg/m^2 and ≥ 32 kg/m^2. 41.8% (330/789) of patients have a BMI of 32 kg/m^2 or more (Table 4.1). The estimated reduction in daily urinary incontinence episodes is 0.45 in patients with a BMI less than 32 kg/m^2 and 0.52 in patients with a BMI of 32 kg/m^2 or more. Both the sponsor's and our analyses do not provide evidence for a BMI effect in the reduction of daily urinary incontinence episodes, the reduction in urinary frequency, and the increase in urine void volume (Tables 4.2 and 4.3).

4.3 Reviewer comments on subgroup analysis

Results of subgroups analyses are not powered to draw a meaningful statistical conclusion, mainly due to small subgroup sizes. The sponsor's conditional/marginal analysis and descriptive statistics are proper for exploration of potential subgroup effects.

There are uncertainties about the drug's effect on urinary frequency in male patients and on urine void volume in non-Caucasian patients due to results that go in the opposite direction for the other subgroups and to the small sample size in these two subgroups.

Table 4.2
CFB at Week 12 (LOCF) for the number of daily urinary frequency in subgroup analyses

	Descriptive statistics			Results from ANCOVA model			
	Value (N)	Mean (SD)		LS Mean (SE)		P-value	
		Placebo	Active	Placebo	Active	Without Transform	RT-2 Transform
Gender	Female (704)	-2.03 (2.82)	-2.76 (3.20)	-2.07 (0.1415)	-2.73 (0.1415)	0.0011	<0.0013
	Male (85)	-1.95 (2.87)	-1.60 (3.19)	-2.03 (0.4250)	-1.51 (0.4845)	0.4238	0.8536
Race	Caucasian (681)	-1.93 (2.79)	-2.55 (3.17)	-1.97 (0.1467)	-2.51 (0.1444)	0.0086	0.0043
	Non-Caucasian (108)	-2.50 (3.00)	-3.49 (3.44)	-2.62 (0.3595)	-3.30 (0.4425)	0.2368	0.1536
Age	< 65 years (506)	-2.31 (2.97)	-3.17 (3.33)	-2.36 (0.1746)	-3.12 (0.1795)	0.0024	0.0010
	≥ 65 years (283)	-1.49 (2.46)	-1.76 (2.79)	-1.53 (0.2088)	-1.72 (0.2066)	0.5369	0.3252
BMI	< 32 kg/m^2 (456)	-2.05 (2.79)	-2.99 (3.25)	-2.13 (0.1820)	-2.91 (0.1804)	0.0026	0.0023
	≥ 32 kg/m^2 (330)	-2.04 (2.86)	-2.16 (3.10)	-2.03 (0.2038)	-2.17 (0.2113)	0.6273	0.3220

Source: Appendices 16.1.9.3.4 through 16.1.9.3.7 of the study report.

Table 4.3
CFB at Week 12 (LOCF) for urine void volume (ml) in subgroup analyses

	Descriptive statistics			Results from ANCOVA model			
	Value (N)	Mean (SD)		LS Mean (SE)		P-value	
		Placebo	Active	Placebo	Active	Without Transform	RT-2 Transform
Gender	Female (694)	3.98 (52.59)	22.67 (67.11)	4.51 (3.1549)	22.13 (3.1640)	<0.0001	0.0006
	Male (84)	2.89 (62.39)	4.90 (42.01)	2.29 (7.4521)	5.70 (8.6058)	0.7650	0.7554
Race	Caucasian (671)	2.17 (54.60)	23.61 (65.08)	2.71 (3.2274)	23.09 (3.1844)	<0.0001	0.0001
	Non-Caucasian (107)	12.36 (48.91)	-0.21 (64.22)	12.33 (6.5263)	-0.17 (8.1189)	0.2329	0.1627
Age	< 65 years (498)	6.64 (54.47)	23.86 (71.40)	6.96 (3.8723)	23.52 (4.0149)	0.0031	0.0589
	≥ 65 years (280)	-1.38 (52.28)	16.15 (53.41)	-0.61 (4.2307)	15.40 (4.1707)	0.0075	0.0062
BMI	< 32 kg/m^2 (450)	1.39 (57.61)	25.08 (60.56)	3.04 (3.8390)	23.46 (3.8056)	0.0002	0.0026
	≥ 32 kg/m^2 (325)	6.96 (48.80)	15.02 (71.52)	6.30 (4.5776)	15.75 (4.7944)	0.1555	0.2824

Source: Appendices 16.1.9.5.4 through 16.1.9.5.7 of the study report.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no major statistical issues with the analysis of efficacy data in this submission. Statistical results from the sponsor's analyses and our alternative analyses using both the mITT and ITT populations were consistent.

5.2 Conclusions and Recommendations

We have reviewed the efficacy data from clinical Study OG05009 submitted in support of the 1 g dose of 10% Oxybutynin Topical Gel once daily for the treatment of overactive bladder. The study was a randomized, double-blind, placebo-control, and parallel group study.

We have verified the sponsor's statistical analyses and have conducted our alternative analyses to further evaluate the efficacy results. Both sets of results support the efficacy of 1 g of 10% Oxybutynin Topical Gel once daily in the reduction of daily urinary incontinence episodes. In addition, the descriptive primary efficacy results by subgroup tended to be consistent but should be interpreted with caution because of the small sample size.

From a statistical perspective, Study OG05009 demonstrates the efficacy of 1 g of 10% Oxybutynin Topical Gel once daily for the treatment of overactive bladder with symptoms of urgency, urge continence, and urinary frequency based on the number of daily urinary in continence episodes. Although the results from the two clinically relevant secondary endpoints of daily urinary frequency and urine void volume are supportive, we recommend that labeling not include their p-values because no adjustment for multiplicity was pre-specified in the protocol and the study was not powered for these two secondary endpoints.

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