

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202513Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type NDA
Application Number(s) 202-513
Priority or Standard Standard

Submit Date(s) December 17, 2010
Received Date(s) February 8, 2011
PDUFA Goal Date December 8, 2011
Division / Office DRUP/ODE 3

Reviewer Name(s) Jonathan P. Jarow, M.D.
Review Completion Date November 30, 2011

Established Name Oxybutynin chloride
(Proposed) Trade Name Anturol
Therapeutic Class Antimuscarinic
Applicant Antares Pharma, Inc.

Formulation(s) Transdermal gel
Dosing Regimen (b) (4) 3 pumps once daily (b) (4)
84 mg)

Indication(s) Treatment of overactive
bladder with symptoms of urge
urinary incontinence, urgency,
and frequency

Intended Population(s) Adults with overactive bladder

Template Version: [March 6, 2009](#)

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	7
1.1	Recommendation on Regulatory Action	7
1.2	Risk Benefit Assessment.....	7
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	9
2.1	Product Information	9
2.2	Tables of Currently Available Treatments for Proposed Indications	10
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues with Consideration to Related Drugs.....	14
2.5	Summary of Presubmission Regulatory Activity Related to Submission	15
3	ETHICS AND GOOD CLINICAL PRACTICES.....	17
3.1	Submission Quality and Integrity	17
3.2	Compliance with Good Clinical Practices	17
3.3	Financial Disclosures.....	17
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	18
4.1	Chemistry Manufacturing and Controls (ONDQA).....	18
4.2	Preclinical Pharmacology/Toxicology	18
4.3	Clinical Pharmacology	18
4.4	Statistics	18
4.5	Consults from Other Divisions	19
4.5.1	Office of Surveillance and Epidemiology (OSE).....	19
4.5.2	Pediatric Review Committee (PeRC)	19
4.5.3	Study Endpoints and Labeling Development Team (SEALD)	19
5	SOURCES OF CLINICAL DATA.....	19
5.1	Tables of Studies/Clinical Trials	20
5.2	Review Strategy	20
5.3	Discussion of Individual Studies/Clinical Trials.....	21
6	REVIEW OF EFFICACY	28
	Efficacy Summary.....	28
6.1	Indication	28
6.1.1	Methods	28
6.1.2	Demographics	29
6.1.3	Subject Disposition.....	30
6.1.4	Analysis of Primary Endpoint(s)	31
6.1.5	Analysis of Secondary Endpoints(s)	34

6.1.6	Other Endpoints	36
6.1.7	Subpopulations	37
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	39
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	39
6.1.10	Additional Efficacy Issues/Analyses	39
7	REVIEW OF SAFETY.....	39
	Safety Summary	39
7.1	Methods.....	39
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	39
7.1.2	Categorization of Adverse Events.....	40
7.1.3	Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence.....	40
7.2	Adequacy of Safety Assessments	40
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	40
7.2.2	Explorations for Dose Response.....	41
7.2.3	Special Animal and/or In Vitro Testing	41
7.2.5	Metabolic, Clearance, and Interaction Workup	41
7.3	Major Safety Results	41
7.3.1	Deaths.....	41
7.3.2	Nonfatal Serious Adverse Events	41
7.3.3	Dropouts and/or Discontinuations	42
7.3.4	Significant Adverse Events	42
7.3.5	Submission Specific Primary Safety Concerns	42
7.4	Supportive Safety Results	46
7.4.1	Common Adverse Events	46
7.4.2	Laboratory Findings	47
7.4.3	Vital Signs	48
7.4.4	Electrocardiograms (ECGs)	48
7.4.5	Special Safety Studies/Clinical Trials	49
7.4.6	Immunogenicity	49
7.5	Other Safety Explorations.....	49
7.5.1	Dose Dependency for Adverse Events	49
7.5.2	Time Dependency for Adverse Events.....	49
7.5.3	Drug-Demographic Interactions	51
7.5.4	Drug-Disease Interactions.....	52
7.5.5	Drug-Drug Interactions.....	52
7.6	Additional Safety Evaluations	52
7.6.1	Human Carcinogenicity	52
7.6.2	Human Reproduction and Pregnancy Data.....	53
7.6.3	Pediatrics and Assessments	53
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	54
7.7	Additional Submissions / Safety Issues	54

8	POSTMARKET EXPERIENCE	54
9	APPENDICES	55
9.2	Labeling Recommendations	55
9.3	Advisory Committee Meeting.....	55

Table of Tables

Table 1: Components of Oxybutynin 3.0% Drug Product.....	9
Table 2: Concentration of Components in Oxybutynin Gel 3.0%, and Maximum Levels Listed in IIG.	10
Table 3: Anticholinergic therapies used for the treatment of overactive bladder.	11
Table 4: Product Information of approved Oxybutynin products.....	13
Table 5: Summary of clinical studies with Oxybutynin gel 3%.....	20
Table 6: Summary of pharmacokinetic data for transdermal oxybutynin gel 3% from Phase 1 and 2 studies.....	24
Table 7: Treatment emergent adverse events of interest by dose reported in Study 20070060 (* denotes significant difference from placebo (p < 0.05)).	26
Table 8: Exposures for various oxybutynin preparations.....	27
Table 9: Subject disposition for Study 20070600.	30
Table 10: Population definitions for Study 20070600.	31
Table 11: Mean change from baseline in weekly urinary incontinence episodes as compared to placebo (source - approved labeling for each product).	34
Table 12: Results of tertiary efficacy endpoints for Study 20070060. * Change from baseline at end of study as compared to placebo arm.	37
Table 13: Summary of extent of exposure in the Phase 3 study and open label extension.....	40
Table 14: Patient demographics and baseline characteristics for Study 20070060 and the open label extension (OLE). Source: ISS page 19.	40
Table 15: Anticholinergic adverse reactions reported for subjects in Study 20070060. Medical officer analysis	42
Table 16: Application site adverse reactions reported for subjects in Study 20070060 reported as events (* reported as subjects). Medical officer analysis.....	44
Table 17: Common adverse reactions in the randomized, double-blind, placebo-controlled 12-week study (20070060) (≥2% and >placebo). Medical officer analysis. .	46

Table of Figures

Figure 1. Age of randomized subjects by gender.	30
Figure 2: Median change from baseline in number of urinary incontinence episodes per week during 12-week double blind treatment periods (mITT population). Source: Study report 20070060 page 69	33
Figure 3: Median number of voids per day during 12-week double blind period (mITT population). Source: Study report 20070060 page 72	35
Figure 4: Median urinary volume per void during 12-week double blind period (mITT population). Source: Study report 20070060 page 74	36
Figure 5: Effect of baseline severity of symptoms, urinary incontinence episodes at baseline (UIE-BASE), upon the primary efficacy endpoint of Study 20070060 (UIE-CHG) by study arm.....	38
Figure 6: Incidence of anticholinergic adverse reactions by preferred application site. Medical officer analysis.	44
Figure 7: There was no difference in the postvoid residual measurements (cc) in each treatment group at the end of study (12 weeks). Medical officer analysis	46
Figure 8: Mean liver function test laboratory result by Visit Number and treatment group in Study 20100060. Medical officer analysis.	47
Figure 9: Vital signs during Study 20070060. Medical officer analysis	48
Figure 10: Time of onset, relative to randomization, of common adverse reactions by treatment arm in Study 20100060. Medical officer analysis.	50
Figure 11: Time of onset of all application site adverse reactions relative to randomization in Study 20100060. Medical officer analysis.	51
Figure 12: Relative risk of all application site reactions (General disorders) and each individual type of reaction comparing skin types: sensitive to normal or insensitive. Medical officer analysis.	52

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, Oxybutynin Gel 3%, three pumps applied once daily (84 mg) 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. (b) (4)

The safety profile of Anturol is comparable to other anticholinergic medications in its class.

The single phase 3 efficacy trial, Study 20070060, demonstrated a p value of less than 0.05 for the primary efficacy endpoint; change from baseline in urinary incontinence episodes per week. The Sponsor’s analysis produced a p value of 0.033 and the FDA analysis was 0.0445. In addition, a statistically significant reduction in daily urinary frequency and increase in volume per void, the key secondary endpoints, was demonstrated for the 84 mg dose with p values less than 0.01. (b) (4)

The point estimate for the effect size attributable to the 84 mg dose is a mean reduction of 1.9 incontinence episodes per week, according to the Sponsor’s analysis. Although this point estimate is small, the effect size of the entire class of anticholinergic medications is not large and the baseline severity of symptoms in Study 20070060 was higher than all previous trials reported to the FDA in the last ten years. The baseline was greater than 40 incontinence episodes per week in Study 20070060 and as will be discussed within this review, a higher baseline severity makes it more difficult to differentiate active drug from placebo.

1.2 Risk Benefit Assessment

A comprehensive review of NDA 202-513 was carried out. This NDA submission has provided evidence from adequate studies that the oxybutynin 3% gel at the 84 mg dose

will have the effect claimed in labeling. This claim is that the topically applied gel is an effective treatment for patients suffering from the symptoms of overactive bladder with primarily urge urinary incontinence. Oxybutynin 3% gel (84 mg) did demonstrate statistically significant ($p = 0.0445$) efficacy for its primary endpoint and all of the secondary efficacy endpoints. In addition, clinical pharmacology studies demonstrated comparable exposure to other approved formulations of oxybutynin. No significant safety issues were detected.

The single phase 3 efficacy trial, Study 20070060, was a 12-week, double-blind, placebo-controlled, randomized trial to evaluate the effectiveness and safety of the 56 mg and 84 mg doses of Oxybutynin 3% gel in patients with overactive bladder. The primary objective was to compare the effects of oxybutynin gel relative to placebo in patients with urge or mixed urinary incontinence with a predominance of urge incontinence episodes. The primary efficacy endpoint was the change from baseline at the end of study in the number of urinary incontinence episodes per week as compared to placebo. Secondary endpoints were change in number of urinations per day and volume of urine per void from baseline as compared to placebo.

The outcome of Study 20070060 was that the mean placebo effect was -20 episodes per week and for 84 mg oxybutynin it was -21.9 ($p=0.0333$) by the Sponsor's analysis. The magnitude of the difference between active drug and placebo was small, reduction of 1.9 episodes per week (reduction of less than 1 urinary incontinence episode every three days). This result is acceptable evidence of a statistically meaningful result.

Oxybutynin 3% gel has been shown to be generally safe for its intended use as recommended in the labeling by all tests reasonably applicable to assessment of safety. The pattern of adverse events seen in the clinical trials submitted is similar to other drugs in the class. The most common adverse events (seen in >2% of subjects) were application site reactions, dry mouth, constipation, nasopharyngitis, eye disorders (dry eye and blurred vision), and urinary tract infections.

The potential for transferring oxybutynin to another individual by direct contact was appropriately evaluated for this drug product. The amount of transfer was negligible if patients cover the application site with clothing prior to contact. There was no significant effect of sunscreen application prior to and subsequent to the administration of drug product upon its absorption.

In summary, the information that has been submitted by the Sponsor is adequate to allow the reasonable conclusion that Oxybutynin 3% gel (84 mg) is a safe and effective treatment for patients with the symptoms of overactive bladder. (b) (4)



1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

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

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in Oxybutynin gel 3.0% is oxybutynin, present in the formulation at a concentration of 3%. Oxybutynin possesses one chiral center and therefore exists in two enantiomeric forms (R and S), with the racemic mixture being used in all currently marketed formulations. Chemically, oxybutynin is d, l (racemic) 4-diethylamino-2-butynyl phenylcyclohexylglycolate, with an empirical formula of C₂₂H₃₁NO₃, MW 357^{(b) (4)}.

Oxybutynin Gel 3% is a transparent, fast-drying, colorless to slightly yellow, non-occlusive gel containing 3.0% w/w oxybutynin free base. The oxybutynin drug product is a homogeneous gel, without particles. The qualitative composition of the commercial drug product, the quality standard and the function of each constituent of the drug product are presented in Table 1. Table 2 provides the quantitative composition of the commercial drug product, and shows that the levels of the excipients are below the maximum levels listed in the Inactive Ingredients Guide (IIG) for comparable dosage forms.

Table 1: Components of Oxybutynin 3.0% Drug Product.

Component and Grade	Regulatory/Safety Status	Function
Oxybutynin base	US DMF	Active ingredient
Diethylene glycol monoethyl ether, NF (DGME)	USP/NF	(b) (4)
(b) (4)	USP/NF	
Hydroxypropyl cellulose (b) (4) NF	USP/NF	
Propylene glycol, USP	USP/NF	
Butylated hydroxytoluene, NF	USP/NF	

Component and Grade	Regulatory/Safety Status	Function
HCl 0.1 M	USP/NF	(b) (4)
Purified water, USP	USP/NF	(b) (4)

Table 2: Concentration of Components in Oxybutynin Gel 3.0%, and Maximum Levels Listed in IIG.

Ingredient	Oxybutynin Gel Concentration (% w/w)	Oxybutynin Gel concentration (mg/g)	Maximum value from IIG for topical or transdermal
Oxybutynin base	3.00	30.0	N/A
Diethylene glycol monoethyl ether, NF (DGME)	(b) (4)	(b) (4)	25.00%
(b) (4)	(b) (4)	(b) (4)	84.95%
Hydroxypropyl cellulose NF	(b) (4)	(b) (4)	4%
Propylene glycol, USP	(b) (4)	(b) (4)	98.09%
Butylated hydroxytoluene, NF	(b) (4)	(b) (4)	2.00%
HCl 0.1 M	(b) (4)	(b) (4)	4.00%
Purified water, USP	(b) (4)	(b) (4)	N/A

2.2 Tables of Currently Available Treatments for Proposed Indications

Overactive bladder (OAB) is defined by the International Continence Society as a symptom complex of urgency usually accompanied by frequency and nocturia, with or without urge incontinence in the absence of urinary tract infection or other obvious pathology. This disorder affects millions of people worldwide and has a significant impact upon quality of life. The symptoms usually occur in the absence of abnormalities on urodynamic testing and this test is not required to establish the diagnosis of OAB. However, when urodynamics are performed and demonstrate an abnormality, the symptoms are then attributed to neurogenic bladder or detrusor hyperreflexia. OAB affects women more often than men with an estimated prevalence of 10 to 15% in women. The management of overactive bladder includes patient education, combined with lifestyle changes, behavioral therapies combined with pelvic floor physical therapy, pharmacologic therapy with antimuscarinics, electrical stimulation (sacral nerve stimulation), botulinum toxin injection of the detrusor, and bladder surgery. Management of the patient with OAB is typically performed in a stepwise fashion in order of risk. Medical therapy, using anticholinergics, is indicated after failure of the more conservative measures of patient education, behavioral therapy and physical therapy. The anticholinergic drug products are available in a variety of formulations

including oral tablets, extended release oral tablets, transdermal patches, and transdermal gel. There are eleven anticholinergic drug products, with just six unique molecular entities, that have been approved for the treatment of OAB (Table 3). The first two anticholinergic medications, approved in the 1950s, are no longer in wide use.

Table 3: Anticholinergic therapies used for the treatment of overactive bladder.

Date of Approval	Brand Name	Active Ingredient	Dose (s)	Sponsor	NDA #
1/27/2009	Gelnique	Oxybutynin chloride 10%	100 mg	Watson	022-204
10/31/2008	Toviaz	Fesoterodine fumarate	4 mg, 8 mg	Schwarz	022-030
8/3/2007	Sanctura XR	Trospium chloride	60 mg	Indevus	022-103
12/22/2004	Enablex	Darifenacin hydrobromide	7.5 mg, 15 mg	Pfizer	021-513
11/19/2004	Vesicare	Solifenacin succinate	5 mg, 10 mg	Yamanouchi	021-518
5/28/2004	Sanctura	Trospium chloride	20 mg bid	Indevus	021-595
2/26/2003	Oxytrol patch	Oxybutynin chloride	3.9 mg/day	Watson	021-351
12/22/2000	Detrol LA	Tolterodine tartrate	4 mg	Pharmacia (Pfizer)	021-228
12/16/1998	Ditropan XL	Oxybutynin chloride	5 mg, 10 mg	Ortho McNeil	020-897
3/25/1998	Detrol*	Tolterodine tartrate	2 mg, 4 mg	Pharmacia (Pfizer)	020-771
7/16/1975	Ditropan	Oxybutynin chloride	5 mg, 10 mg	Ortho McNeil	017-577
2/2/1955	Levsin, Cystospaz	Hyoscyamine sulfate	0.125 mg	Redondo	009-800
4/2/1953	Pro-Banthine	Propantheline bromide	7.5 mg, 15 mg	Shire	008-732

The primary efficacy endpoints used in the evaluation of anticholinergic therapies for OAB include change from baseline (as compared to placebo) of weekly urinary incontinence episodes and daily urinary frequency, in that order. A systematic review of the outcomes of anticholinergic drug trials reveals an absolute mean improvement of 3.3 in incontinence episodes per week and 0.7 voids per day as compared to placebo. Moreover, anticholinergic therapy produces a 64% increase in cure rate (no urinary incontinence and urinary frequency less than 8 per day) as compared to placebo. The absolute treatment benefit over placebo is small due to the large placebo effect. The absolute change from baseline averaged 15 for drug and 11.7 for incontinence episodes

per week, which is what a patient on drug could expect. The clinically meaningful threshold calculated on the basis of a global assessment question in five separate studies was 14.8 urinary incontinence episodes per week and active drug beat this threshold. Although there are no head-to-head comparison studies, no compelling evidence exists that would indicate that one antimuscarinic agent for OAB is superior to another in efficacy.

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 consistent 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 formulations, 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, transdermal formulations produce application site reactions and these are the most frequently reported adverse reactions and a common reason for treatment discontinuation.

2.3 Availability of Proposed Active Ingredient in the United States

Oxybutynin chloride is currently 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 4. The approval history of these products is as 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 5, 10, and 15 mg extended release (Ditropan XL®) 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.
- NDA 22-204 for oxybutynin chloride gel 10% (Gelnique®) was approved for use in adults in January 2009.

Table 4: Product Information of approved Oxybutynin products.

Trade Name	Ditropan®	Ditropan XL®	Oxytrol®	Gelnique®
Formulation	Oral tablet and syrup (IR)	Oral tablet (ER)	Transdermal patch system	Topical gel
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”	“... 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 Adults: Start with 2.5 mg bid to tid, increase in increments up to maximum of 20 mg/day in divided doses as needed Pediatric patients: 5 mg bid, up to maximum of 5 mg	5 mg, 10 mg, 15 mg Adults: Start with 5 or 10 mg once daily, increase in 5 mg increments as necessary (maximum of 30 mg/day) Pediatric patients (≥ 6 years): 5 mg	3.9 mg/day (39 cm ² patch) Change one system (3.9 mg/day) every 3 to 4 days	Apply contents of one sachet (100 mg) once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs.

Trade Name	Ditropan®	Ditropan XL®	Oxytrol®	Gelnique®
	tid	once daily, increase in 5 mg increments as needed (maximum of 20 mg/day)		
Intended population	Adult and pediatric patients (≥ 6 years) with bladder instability due to detrusor instability or neurogenic bladder	Same as Ditropan®	Adults with OAB	Adults with OAB

Source: Product labeling for Ditropan®, Ditropan XL®, Oxytrol®, and Gelnique®.

2.4 Important Safety Issues with Consideration to Related Drugs

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 Summary of Presubmission Regulatory Activity Related to Submission

A pre-IND meeting was held with the sponsor on February 9, 2005. At that time the sponsor asked the Division to address the feasibility of a 505(b)(2) pathway for product development using the transdermal patch (Oxytrol) as the reference. The sponsor opened IND 70,527 Oxybutynin transdermal gel 3% on March 11, 2005. The opening study was a Phase 2 dose-ranging study evaluating single and multiple-dose pharmacokinetics of oxybutynin gel 3%. The initial proposed study was modified based upon FDA suggestions to include a longer duration of therapy (20 rather than 10 days), a third dose (60 mg in addition to 42 and 84 mg), and increased sample size.

An end of Phase 2 meeting was held on May of 2006 during which the Division recommended that the sponsor follow a 505(b)(1) pathway for product development. The meeting minutes state that “the Division recommends that two Phase 3 studies be performed. Alternatively, one study which demonstrates conclusive results could be submitted”. The sponsor requested clarification of “conclusive” and the Division’s response was that for a study “to be considered conclusive, a single efficacy trial would have to be both *clinically and statistically significant*” and that “the definition of “clinically significant” will be a review issue.” In addition, “Borderline significant results from a single efficacy trial can pose review issues and is a risk a Sponsor assumes when conducting only a single study.” The Division stated that the indication statement in the Sponsor’s proposed labeling would be consistent with the triad symptomatology (incontinence, urgency, and frequency) currently approved for other overactive bladder products. The Division also clarified that the secondary endpoint, volume voided per micturition, could be included in the product labeling as it is for currently approved overactive bladder drug products. At least 50 subjects should complete 6 months of active treatment (3 months trial plus 3 months open-label) to assess skin tolerability.

A special protocol assessment for a Phase 3 protocol was submitted by the sponsor in August, 2006. A single dose of 84 mg/day was compared to placebo over a twelve week period with a primary endpoint of change from baseline of weekly incontinence episodes calculated from a 3 day diary. Sample size was based on the assumption that with a standard deviation of 17 episodes per week and 180 patients per treatment group, a difference of 6 episodes per week between treatment groups could be detected with 90% power. Randomization of 360 patients (180 per arm) should be sufficient to ensure that data will be obtained for at least 169 patients per treatment arm completing the trial (6% missing data).

Several revisions, including the addition of a second, lower, active dose, were requested by the Division and a revised protocol was submitted in May, 2007. In addition, the sponsor completed a Phase 1 bioequivalence study to assess the effect of site of application upon pharmacokinetics. Review of the data revealed that exposures were significantly higher when the product was applied to shoulders and arms (132% for Cmax) and the Division recommended limiting application of the gel to only the abdomen and thighs.

At the time of the review of the revised protocol submitted by the Sponsor, the clinical medical reviewer stated the following requiring the level of evidence necessary to support the claim of efficacy in a submitted NDA, "Conclusive results of a single Phase 3 trial, along with supportive data from Phase 2, could constitute confirmatory evidence." The Phase 2 PK study discussed above compared serum levels of oxybutynin and DEO following application of oxybutynin gel with available data on the pharmacokinetics of the oxybutynin transdermal patch (Oxytrol) and oral extended release oxybutynin. These levels were comparable and, in this reviewer's opinion, would constitute adequate confirmatory evidence. As the Division stated at the May 2, 2006, EOP2 meeting, "one [Phase 3] study which demonstrates conclusive results could be submitted [to support an NDA]. To be considered conclusive, a single efficacy trial would have to be both clinically and statistically significant. The definition of 'clinically significant' will be a review issue".

In May of 2008, the sponsor requested further revisions to the statistical analysis plan of their protocol. A request for an interim analysis was rejected by the Division. Imputation of missing week 12 urinary incontinence episodes using modeling incorporating interim and baseline data was approved.

In the summer of 2008, the sponsor identified trace levels of (b) (4) (b) (4) a potential carcinogen, in the oxybutynin gel product and held two conference calls with the Division. (b) (4)

One hundred and thirty subjects had already completed the study with the original formulation at that point. The subsequent 480 subjects enrolled received the to-be-marketed formulation (b) (4) The Division

recommended that “a single dose in vivo bioequivalence study comparing the original (b) (4) versus the reformulated (b) (4) oxybutynin gel products should be conducted to allow bridging of the existing data to the new formulation. Due to a change in a critical component of the gel product, results obtained from any phase 1 studies related to transfer, wash-off, sunscreen interaction assessments etc may not be applicable to the new formulation and therefore may need to be repeated.” After completion of the bioequivalence study, the Division agreed to allow pooling of data for the two formulations in the single Phase 3 study, stipulating that the formulation used should be flagged for each subject.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Central laboratory: In Study 20070060, laboratory testing for safety parameters was performed by (b) (4). 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).

Data Quality: Subject source notes were entered into an electronic data capture online database system by the investigator or designee. Preprogramming allowed for alerts for out of range values, missing data, and inconsistent data.

Site Monitoring: Study 20070060 study sites were monitored and audited by (b) (4). Audit certificates indicating GCP compliance were submitted for 4 of the 63 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.

3.2 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

.3.3 Financial Disclosures

Form FDA 3454, dated December 17, 2010, and signed by Kaushik J. Dave, Ph.D., Senior Vice President Product Development, Antares Pharma, Inc., was submitted.

Financial disclosure documents were submitted only for clinical investigators (principal and sub-investigators) for Study 20070060; this approach is acceptable, because the approval of this NDA was based primarily on this study.

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (ONDQA)

The reviewer from ONDQA recommends approval.

4.2 Preclinical Pharmacology/Toxicology

The reviewer from Nonclinical stated that “Oxybutynin is a well characterized muscarinic antagonist, approved in oral and dermal forms for OAB. The pharmacokinetics and metabolism of oxybutynin are known in humans following both oral and transdermal administration, as is the safety profile of the drug” and “There is no impediment to approval of this application from a Pharmacology/Toxicology perspective.”

4.3 Clinical Pharmacology

The reviewer from clinical pharmacology recommends approval pending agreement on labeling. The clinical pharmacology reviewer concludes that the Sponsor has demonstrated that the systemic exposure of oxybutynin from Anturol and the currently approved Oxybutynin topical gel product are similar. The reviewer from clinical pharmacology did not recommend any Phase 4 requirements.

4.4 Statistics

The reviewer from biostatistics recommends approval of the 84 mg dose (b) (4)

the primary (urinary incontinence) and secondary endpoints (urinary frequency and volume per void) for the 84 mg dosage did meet the pre-specified statistical goals.

4.5 Consults from Other Divisions

4.5.1 Office of Surveillance and Epidemiology (OSE)

- Division of Medication Error Prevention and Analysis (DMEPA): DMEPA accepts the trade name of “Anturol”. After reviewing product labeling, DMEPA recommended some changes to reduce the risk of medication errors.
- Division of Risk Management (DRISK): DRISK recommended changes to the labeling that were agreed to by the Sponsor.

4.5.2 Pediatric Review Committee (PeRC)

- A full pediatric waiver was granted.

4.5.3 Study Endpoints and Labeling Development Team (SEALD)

- SEALD recommended changes to the labeling that were agreed to by the Sponsor.

5 Sources of Clinical Data

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

- Overview section, clinical summaries, and integrated summary of safety
- Clinical safety and efficacy: Study 20070060 (“A Double-Blind, Randomized, Parallel, Placebo-Controlled, Multicenter Study Evaluating the Effect of Treatment with Topically Administered Oxybutynin Gel in Patients with Urinary Frequency and Urge and Mixed Urinary Incontinence with a Predominance of Urge Incontinence Episodes with an Open-Label Extension”)
- Pharmacokinetics: Study 1034-PhII (“A Phase II, Single-Center, Open-label, parallel, three treatment, single period, randomized, single and multiple-dose pharmacokinetic study of oxybutynin gel in healthy volunteers”) and Study SCO 5432 (“Single-center, multiple-dose, open-label, randomized, 2-period cross-over bioequivalence study on two 3 % gel formulations of oxybutynin at a dosage of 84 mg daily in healthy subjects”)
- Phase 1 studies Study SCO 5486 (person-to-person transference), Study SCO 5487 (effect of application of sunscreen), and Study SCO 5488 (effect of showering).
- 120-Day Safety Update
- IND 70,527: Annual reports

5.1 Tables of Studies/Clinical Trials

Table 5 summarizes the clinical studies used to support the safety and efficacy of oxybutynin gel 3%. The only study performed in the U.S. under IND 70,527 was the Phase 3 efficacy and safety trial (Study 20070060). The remaining studies were performed outside the U.S.

Table 5: Summary of clinical studies with Oxybutynin gel 3%.

Type of Study	Objective	Oxybutynin Gel 3% Daily Dose	Formulation	Duration of Rx	# of Subjects (M/F)	Age Range (years)
Phase 1			(b) (4)		Healthy Subjects	
OPK2 (SCO 5157)	Pilot PK	2 g (60 mg) 1 g (30 mg)		7 doses	8 (0/8)	27-47
OXBTN/2006223	Application site	2.8 g (84 mg)		3 doses	30 (6/24)	18-42
SCO 5432	Bioequivalence	2.8 g (84 mg)		14 days	58 (26/32)	22-52
SCO 5488	Effect of Showering	2.8 g (84 mg)		19 days	22 (13/9)	21-53
SCO 5486	Transfer potential	2.8 g (84 mg)		2 doses	28 (14 treated) (5/9)	24-52
SCO 5487	Sunscreen	2.8 g (84 mg)		3 doses	20 (6/14)	20-51
Phase 2					Healthy Subjects	
1034-PhII	Dose-ranging PK	1.4 g (42 mg) 2 g (60 mg) 2.8 g (84 mg)		20 days	48 (12/36)	19-53
Phase 3					OAB Subjects	
20070060	Efficacy/Safety	Placebo 1.9 g (56 mg) 2.8 g (84 mg)		12 weeks	626 (84/542)	19-89
20070060 OLE	Open-label Extension	2.8 g (84 mg)		24 weeks	78	

Source: Synopses of Individual Studies, Module 2.7.6

5.2 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 20070060; the safety review included the integrated Study 20070060, the 5 integrated phase 1 studies, the 2 integrated phase 2 studies, and the non-integrated person-to-person transfer study.
- The focus of the efficacy and safety review was Study 20070060 double-blind period. This was the only adequate and well-controlled clinical study appropriately designed to assess drug effect on both safety and efficacy.
- Comparative PK studies (1034-PhII, OXPK2, OXBTN/2006/223 and SCO 5432) were reviewed in detail in the clinical pharmacology section to assess the similarity of PK parameters between 1 g 10% OTG and Gelnique.
- The person-to-person transfer study (SCO 5486), the sunscreen study (SCO 5487), and the showering study (SCO 5488) were reviewed in detail.
- Independent analyses of the data sets of the original efficacy and safety variables were conducted throughout the clinical review to explore certain safety/efficacy issues of interest and to verify sponsor's findings.

5.3 Discussion of Individual Studies/Clinical Trials

Ex vivo studies – (Studies 368/03 and 343/03)

The sponsor conducted three *ex vivo* studies to characterize the rate and extent of skin penetration of oxybutynin. The first two (Studies 368/03 and 343/03) were conducted (b) (4) upon human cadaver skin and pig, respectively. Both studies compared oxybutynin gel 3% to Oxytrol. The first study assessed dose escalation. By increasing the loading dose of the gel five-fold, there was only a 3.4-fold increase in absorption by pig skin. The second study in human skin showed that the gel formulation has decreased bioavailability as compared to the patch (2.4% versus 3.7%) and that at least 54 mg would be necessary to achieve comparable plasma levels of the approved 39 cm² Oxytrol patch (3 ng/ml). The third *ex vivo* study (Study 932/09) was performed using the new formulation (b) (4) in fresh frozen human skin. Gelnique was the comparator instead of Oxytrol. This *ex vivo* study suggested that 2.3 g of drug product (b) (4) (69 mg of oxybutynin) should be bioequivalent to the approved 1 gm of Gelnique (100 mg oxybutynin).

Reviewer's comment: *These ex vivo studies provide confirmatory evidence of efficacy and safety by creating a bridge to already approved and marketed products deemed to be safe and effective by the FDA.*

Single dose and multiple dose pharmacokinetic studies (OXPK2 & 1034-PHII)

The first in human Phase 1 dose escalation pharmacokinetic study (OXPK2) using two doses (1 and 2 g) of 3% gel was performed in Hamburg, Germany in 8 healthy female volunteers. An active comparator was not used. The study found that serum levels of oxybutynin and desethyloxybutynin (DEO) were comparable to that reported in the

labeling for Oxytrol. In addition, linear pharmacokinetics was observed allowing for dose extrapolation. This study was performed using the initial [REDACTED] (b) (4) formulation.

A phase 2 pharmacokinetic study (1034-PHII) in 48 healthy volunteers was performed in Germany. A parallel design of three groups receiving 42 mg, 60 mg, and 84 mg daily dosages of oxybutynin gel 3% [REDACTED] (b) (4) was performed over a 20 day period. The results of this study showed minimal to no effect of gender upon PK parameters. The results were consistent with but not proof positive of dose proportionality and PK linearity. The main factor for limiting exposure to oxybutynin is skin permeability, thus increasing the concentration would not result in substantially higher oxybutynin concentrations.

Reviewer's comment: *Using this study as confirmatory evidence for efficacy is hampered by the lack of an active approved comparator in the study. Intra-subject and inter-subject variability also may affect the results.*

Application site study (OXBTN/2006/223)

A single dose, open-label comparative pharmacokinetic study was performed in India using healthy volunteers (n = 30) to study the effect of application site upon pharmacokinetics. Of note, only 25 subjects (83%) completed the study, three subjects were withdrawn due to non-compliance and two due to adverse events (fever). A single dose of 2.8 gm (84 mg oxybutynin) was administered daily, the abdomen was the reference site and the thighs and shoulder/upper arms were the test sites. The results of this study showed that abdomen and thigh had equivalent PK parameters, whereas the AUC_t and C_{max} for the shoulder site were 114% and 133% higher than abdomen, respectively. In contrast, the C_{max} for desethyloxybutynin at both the thigh and shoulder sites were lower when administered at the abdomen (84% and 92%, respectively).

Reviewer's comment: *The point estimates and variability of the pharmacokinetic parameters were much higher than seen in the studies performed in Germany. It is not clear whether this was due to a difference in ethnicity, compliance, or some unknown factors. In conclusion, concerns about the variability led to the recommendation that the only sites that were acceptable were the abdomen and thighs.*

Bridging pharmacokinetic study of new formulation [REDACTED] (b) (4) (SCO 5432)

An open-label, 2-period, crossover study was performed to determine bioequivalence between the two formulations [REDACTED] (b) (4) in Hamburg, Germany. Fifty-eight healthy subjects were enrolled and 54 completed the study. Standard bioequivalence parameters were applied for this study. The new formulation [REDACTED] (b) (4) had an AUC that was 16% higher than the original and a C_{max} that was 24% higher. The 90%

confidence interval was outside the pre-specified criteria for bioequivalence. Thus, the new formulation significantly increases the exposure of oxybutynin and is not bioequivalent with the original formulation.

Reviewer's comment: *One hundred and thirty subjects received the first formulation (b) (4). These subjects were included in all analyses of efficacy and safety performed by the Sponsor. The "assumption" was that the 130 subjects exposed to the first formulation had lower exposure, and therefore, lower efficacy. Thus, the lack of bioequivalence between the two formulations was expected to reduce the chances of demonstrating efficacy. Thus, the inclusion of the subjects receiving a formulation with a lower exposure were assumed to reduce the estimate of efficacy rather than increase it. In the meantime, the subjects were to be flagged in the data tables so that the safety analysis could differentiate between the two formulations.*

Showering study (SCO 5488)

An open-label, 4-period, crossover study of the effect of showering upon the pharmacokinetics of transdermal oxybutynin gel 3% was performed in Germany using the formulation (b) (4). Twenty-two healthy subjects completed all four treatment periods comparing steady state PK of abdominal skin application of 2.8 g Anturol (84 mg oxybutynin) without showering to showering 1, 2, and 6 hours after application. All subjects performed daily application without showering for three consecutive days and then four further days with or without showering at the designated times. Thus, the steady state measurements at one week reflected seven days exposure with the last four days showering at a specified time after application of drug product. There was no effect of showering two or six hours after application of the drug product. Showering one hour after application lowered the AUC by 15% but did not affect Cmax.

Reviewer's Comment: *From a clinical perspective, the effect of showering within two hours after application upon the bioavailability of the drug product will be dealt with in product and patient labeling.*

Table 6: Summary of pharmacokinetic data for transdermal oxybutynin gel 3% from Phase 1 and 2 studies.

Study	OXPK2		OXBTN/2006/223	
Dose	Anturol (60 mg)		Anturol (84 mg)	
Subjects	8 healthy female subjects		25 healthy subjects	
Duration	7 days		Single Dose	
Location	Germany		India	
	Oxybutynin	DEO	Oxybutynin	DEO
AUC _t (ng ml/hr)	164 ± 55	149 ± 101	284 ± 108	636 ± 289
Cavg (ng/ml)	6.84 ± 2.3	6.2 ± 4.2	--	--
Cmax (ng/ml)	9.34 ± 3.43	7.5 ± 5.3	6.3 ± 3.5	12.5 ± 14.5
Study	SCO 5432		1034-PHII	
Dose	Anturol (84 mg)		Anturol (84 mg)	
Subjects	54 healthy subjects		48 healthy subjects	
Duration	7 days		20 days	
Location	Germany		Germany	
	Oxybutynin	DEO	Oxybutynin	DEO
AUC _t (ng ml/hr)	156 ± 63	158 ± 89	130 ± 38	73 ± 32
Cavg (ng/ml)	6.5 ± 2.6	6.6 ± 3.7	5.4 ± 1.6	3.0 ± 1.3
Cmax (ng/ml)	9.7 ± 5.1	8.9 ± 5.3	7.3 ± 2.3	4.6 ± 3.9
Study	SCO 5488		SCO 5487	
Dose	Anturol (84 mg)		Anturol (84 mg)	
Subjects	22 healthy subjects		20 healthy subjects	
Duration	7 days		Single dose	
Location	Germany		Germany	
	Oxybutynin	DEO	Oxybutynin	DEO
AUC _t (ng ml/hr)	220 ± 111	---	151 ± 59	---
Cavg (ng/ml)	9.2 ± 4.6	---	---	---
Cmax (ng/ml)	14.3 ± 9	---	5 ± 2.2	---

Sunscreen study (SCO 5487)

An open-label, three-period, single dose, crossover study was performed upon 20 healthy subjects in Germany to determine the effect of sunscreen application upon the bioavailability of a single dose of transdermal oxybutynin gel. Application of sunscreen 30 minutes prior to or 30 minutes following application of 84 mg oxybutynin gel

(b) (4) to the same area (abdomen) was compared to a single dose. No effect was observed for sunscreen application before drug product but there was a lowering of the C_{max} when sunscreen was applied 30 minutes after.

Person-to-person Transfer study (SCO 5486)

A single dose, two-period, crossover study was performed in Germany to assess the potential of drug transfer through skin exposure from treated to untreated subjects. Fourteen healthy couples were enrolled (28 subjects). The formulation (b) (4) was studied. One partner applied 2.8 g of drug product to an arm and two hours later engaged in 15 minutes of continuous contact, arm to arm, with the untreated partner. Treated partners' arms were bare and the untreated were randomized to bare or clothed for the two periods. There was a two week wash-out phase between treatments. The exposure for untreated subjects with bare arm contact was approximately 20% that of a treated subject. There was essentially no exposure by transfer when the untreated partner's arm was covered (clothed) in terms of measurable serum levels of oxybutynin.

Reviewer's Comment: *The effect of potential transfer with bare skin contact will be dealt with in product labeling.*

Phase 3 clinical efficacy and safety study (Study 20070060)

A Phase 3 double-blind randomized controlled trial was performed at 63 U.S. sites to assess the efficacy and safety of two doses (56 mg and 84 mg) of transdermal oxybutynin gel 3% as compared to placebo. The trial was structured very similar to that of trials performed for the approval of other anticholinergic medications for the treatment of overactive bladder. There was no placebo run-in period. Subjects were screened based on baseline severity of urinary incontinence and urinary frequency. A total of 626 symptomatic (≥ 3 months duration) adult subjects were randomized to the three arms and 493 (79%) completed the 12 week double blind phase of the trial. Eighty-six subjects continued in an open label extension trial described below. The primary efficacy measure was change from baseline at week 12 as compared to placebo in number of weekly urinary incontinence episodes. These data were based on a three day diary that was extrapolated to a week. Secondary efficacy end points included change from baseline at week 12 as compared with placebo in number of voids per day and change in urinary volume. Other safety outcome parameters assessed included application site inspections; patient perception of their condition based upon several patient-reported outcome instruments; and adverse events.

As previously stated, the formulation of the product was changed in the midst of the Phase 3 trial after 130 subjects were already randomized and had completed the study. The remainder of the subjects received the new formulation (to be marketed) (b) (4). (b) (4). A bridging pharmacokinetic bioequivalence study was performed (SCO 5432) prior to proceeding. However, this bridging study failed to meet the pre-

specified criteria for bioequivalence. The Division granted approval to combine the data sets for the two formulations.

A statistically significant difference from placebo was documented in the primary efficacy end point for only the 84 mg dose ($p = 0.0445$). The absolute difference of urinary incontinence episodes per week from placebo was 1.9 using the Sponsor's analysis and 2.3 using LOCF by biostatistics. The efficacy of the 84 mg dose was confirmed by a statistically significant outcome with the secondary endpoints and pharmacokinetic data showing comparable exposure with already approved oxybutynin products.

The 56 mg dose did not meet the pre-specified primary and secondary endpoints and therefore efficacy for this dose could not be confirmed.

There were no deaths and only nine serious adverse reactions; none of which appeared related to the study drug. There were 672 treatment emergent adverse events reported in 52% of the population (see Table 7). The most common adverse events were application site reactions and dry mouth. Both of these were statistically higher than placebo. The cumulative incidence of constipation and dry mouth was slightly higher for the higher dose but application site reactions did not appear to be dose dependent.

Table 7: Treatment emergent adverse events of interest by dose reported in Study 20070060 (* denotes significant difference from placebo ($p < 0.05$)).

	Oxybutynin 84 mg/day (N=214)	Oxybutynin 56 mg/day (N=210)	Placebo (N=202)
Subjects \geq 1 TEAE	114 (53)	120 (57)	91 (45)*
Dry Mouth	26 (12)	23(11)	10 (5)*
Constipation	8 (4)	3 (1)	5 (3)
Application site	24 (11)	25 (12)	4 (2)*
Respiratory	12 (6)	13 (6)	10 (5)
Migraine	0 (0)	0 (0)	3 (2)*
Eye Disorders	10 (5)	7 (3)	5 (3)
Urinary Retention	0 (0)	0 (0)	3 (2)*

Reviewer's Comment: *This single phase 3 study demonstrates statistical evidence of efficacy, defined as a p value of less than 0.05, for the 84 mg dose only, although from a the results are borderline from a clinical perspective. The safety profile for the 84 mg dose is comparable to that of already approved formulations of oxybutynin chloride.*

Open label skin tolerance extension study

An open-label extension of the single Phase 3 efficacy and safety study (20070060) was performed using a daily dose of oxybutynin gel (84 mg), (b) (4) for 24 weeks. All subjects were recruited after satisfactorily completing 12 weeks of double-blind therapy. Of the 77 subjects who entered the open-label extension, only 63 (82%) completed the six months of therapy. Four subjects discontinued due to adverse events, four were lost to follow up, and six withdrew consent. Application site reactions, generally mild to moderate in severity, occurred in two subjects during the open label extension and none of these subjects dropped out of the study. Other frequent treatment emergent adverse events were urinary tract infections and nasopharyngitis, roughly 5% each.

Systemic exposures to Oxybutynin and the active metabolite DEO

Table 8 lists the systemic exposure to oxybutynin and its active metabolite, DEO, amongst various approved oxybutynin products on the market today. The ratio of DEO to oxybutynin is much higher for the oral preparations than for the topical, 4 versus 1. The exposure to both oxybutynin and DEO with Anturol 84 mg is very similar to that of Gelnique 100 mg.

Table 8: Exposures for various oxybutynin preparations.

Parameter	Analyte	Ditropan IR (5 mg tid)	Ditropan XL (15 mg)	Oxytrol TDS (3.9 cm ²)	Gelnique (100 mg)	Anturol (84 mg)
AUC _t (ng hr/ml)	Oxy	80.6 ± 43	109 ± 43		113 ± 58	156 ± 63
	DEO	483 ± 281	304 ± 145		109 ± 87	158 ± 89
C _{avg} (ng/ml)	Oxy			3.1 ± 0.7	4.7 ± 2.4	6.5 ± 2.6
	DEO				4.5 ± 3.6	6.6 ± 3.7
C _{max} (ng/ml)	Oxy	12 ± 4	6.7 ± 2.1	4.2 ± 1	6.8 ± 3.9	9.7 ± 5.1
	DEO	45 ± 20	23 ± 14	4.9 ± 2	5.4 ± 4	8.9 ± 5.3
DEO/Oxy		4	3.4	1.2	0.79	0.92
Total (DEO+Oxy)		564	413		222	314

6 Review of Efficacy

Efficacy Summary

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 therapy with Anturol resulted in clinically and statistically significant improvement in OAB symptoms over placebo. The efficacy assessment was based entirely on the findings of the single Phase 3 Study 20070060, as this was the only study in the clinical development that evaluated clinical outcomes. The efficacy findings of Study 20070060 are reviewed in detail in this section. Independent analyses of the submitted data sets of Study 20070060 were conducted to verify the sponsor’s efficacy findings; and the treatment effect of OTG was compared to those of other approved products for OAB.

Study 20070060 was a multi-center, prospective, double blind, placebo controlled trial of safety and efficacy of two dosages of transdermal oxybutynin gel 3%, 84 mg and 56 mg, in 626 adult subjects with symptoms of OAB for at least three months duration.

Significant inclusion and exclusion criteria are as follows.

Inclusion

- History of ≥ 1 urge episodes per day and ≥ 8 voids per day
- Having ≥ 1 urinary incontinence episode per day (primarily urge)
- Previously benefited from anticholinergic therapy or were treatment naïve

Exclusion

- Concurrent use of herbal medications, cytochrome P450 3A inhibitors, estrogen, or diuretics
- Stress incontinence
- PVR > 200 ml
- History of urinary retention, gastric retention, narrow angle glaucoma, or > 3 treated UTI in past year
- Lower urinary tract surgery within last six months
- Diagnosis of IC or painful bladder syndrome

Reviewer’s comment: *Recruiting too many subjects with a prior positive response to anticholinergics could potentially inflate both the efficacy and safety. However, only 14% of subjects randomized had prior anticholinergic therapy. Excluding subjects*

taking estrogen may limit the general applicability of these findings since many patients with OAB are post-menopausal women.

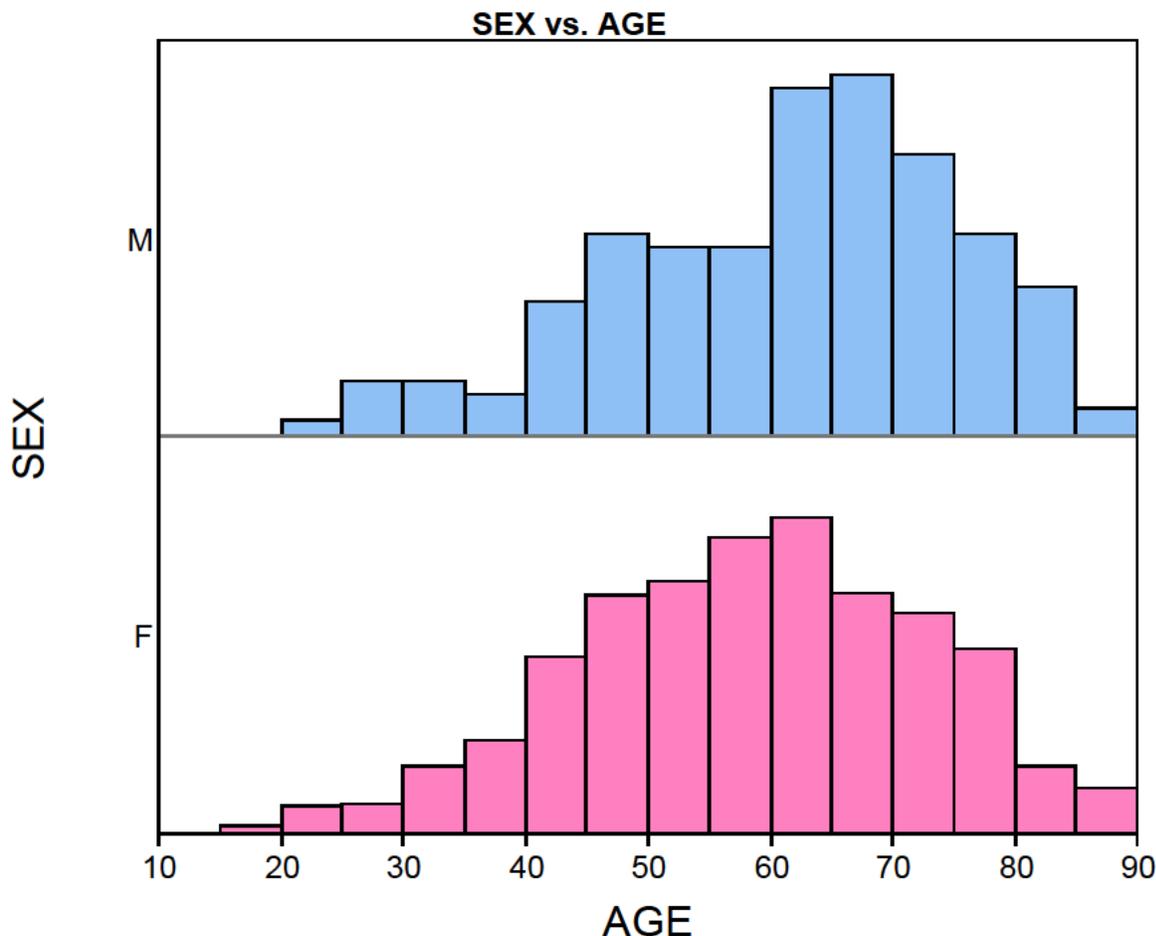
The primary efficacy endpoint was change in weekly urinary incontinence episodes from baseline to week 12 for the 84 mg dose as compared to placebo in the ITT population. The 56 mg dose was to be compared only if the 84 mg dose analysis was significant. Subjects completed a voiding diary for three days at the following time points; baseline, 2, 4, 8 and 12 weeks. Voided volumes were collected for two days at baseline, week 4 and week 12. Two patient reported instruments were administered, Incontinence Impact questionnaire and the Patient Perception of Bladder Condition at baseline and all subsequent visits. The Patient Global Impression of Improvement was administered at the end of study.

Reviewer's comment: *The questionnaires employed in this study may be useful for exploratory analyses but have not been validated adequately to be used in product labeling.*

6.1.2 Demographics

There were 626 patients randomized into the study at 63 study sites. The mean age of the subjects was 58.8 years and the range was 19 to 89 years. The majority of subjects were white (542 subjects [87%]) and female (542 subjects [87%]). Three quarters of the subjects (469) were white females and their mean age was 60 years. The mean age of the men in the study was slightly higher than the women (Figure 1), 61 versus 58 ($p = 0.009$). Overall mean (SD) BMI was 31.2 (7.4) kg/m^2 . These demographic characteristics were balanced across the three treatment groups. Only 89 subjects (14%) were previous anticholinergic medication responders, the remainder were treatment naïve.

Figure 1. Age of randomized subjects by gender.



6.1.3 Subject Disposition

Of the total of 626 subjects with stable symptoms of OAB randomized in the study, 493 (79%) completed the study. Adverse events accounted for 38% of the 133 subjects that discontinued drug and there was no difference between the treatment groups. In contrast, there was an imbalance in discontinuation for “patient decision” amongst the treatment groups ($p = 0.003$) with the Placebo group having the highest rate.

Table 9: Subject disposition for Study 20070600.

	Treatment Groups			Overall n (%)
	Oxybutynin 84 mg n (%)	Oxybutynin 56 mg n (%)	Placebo n (%)	
Randomized	214	210	202	626
Completers	177 (83)	165 (79)	151 (75)	493 (79)
Discontinuations				

	Noncompliance	3 (1)	5 (2)	1 (0.5)	9 (1)
	Adverse Events	19 (9)	21 (10)	10 (5)	50 (8)
	Protocol Deviation	0	3 (1)	2 (1)	5 (1)
	Lost to Follow up	2 (1)	2 (1)	7 (3)	11 (2)
	Patient Decision	12 (6)	10 (5)	25 (12)	47 (8)
	Other	1 (0.5)	4 (2)	6 (3)	11 (2)

The randomized and safety populations included all 626 subjects. The mITT and per protocol populations included 532 (85%) and 493 (79%) subjects, respectively.

Table 10: Population definitions for Study 20070600.

Population	Criteria	N (%)
Randomized/ ITT/Safety	Patients who were randomized in the study and received at least one dose of any study drug.	626 (100)
mITT	Properly randomized; Received at least one dose of study drug; Had completed urinary diary on 3 consecutive days at Baseline and at least once at post-Baseline period; Had an average of at least 1 urinary incontinence episode per day and an average of 8 or more voids per day at Baseline; Had not used any prohibited prior and/or concomitant medication.	532 (85)
Per Protocol	Use of prohibited prior and/or concomitant medication(s); Violation of inclusion/exclusion criteria; Significant protocol violation(s); Missing Baseline data; No data for post-Baseline visits; Unacceptable levels of compliance to dosing; Unacceptable diary completion; Missing study visits; Significant pre-existing medical conditions and procedures.	384 (61)

6.1.4 Analysis of Primary Endpoint(s)

The data were analyzed according to the statistical plan submitted by the sponsor. The mITT population was chosen by the Sponsor to assess efficacy but the biostatistician analyzed the data using the ITT population. The primary endpoint was change from baseline to week 12 in the number of urinary incontinence episodes in the active treated groups as compared to placebo. Missing data for the primary endpoint, urinary incontinence episodes at week 12, were imputed using a mixed model repeated measures approach. Estimates were from a repeated measurement model with fixed effects for Baseline UIE rank, treatment, study week, and study week by treatment interaction, random effect for pooled site. Covariance matrices for measurements from the same patients were assumed to be unstructured. Estimates for treatment effect size

were originally planned to use the least square means from the mixed model with untransformed data. Because the data were not distributed normally, and the fact that statistical significance of treatment effect was based on rank transformed data, it was decided that non-parametric estimates of median were more appropriate. The treatment effect sizes were reported as median and confidence intervals based on Hodges-Lehmann's method (Figure 2).

At baseline, the mean and median weekly urinary incontinence episodes were slightly lower in the oxybutynin 84 mg group compared to the other treatment groups; median values were 37.3 episodes in the oxybutynin 84 mg group, (b) (4), and 42.0 episodes in the placebo group. At the end of study (Week 12), median reductions (improvement) from baseline in weekly urinary incontinence episodes were -18.7 (b) (4) episodes experienced by patients in the oxybutynin 84 mg (b) (4), compared with -16.3 episodes in the placebo group.

In the Sponsor's analysis of the reductions from baseline in mean weekly urinary incontinence episodes (using rank transformation on values) the least square mean differences between oxybutynin 84 mg and placebo (difference: -26.5, $p = 0.0333$) (b) (4) were statistically significant, in favor of oxybutynin. The analysis by biostats confirmed statistical significance for the 84 mg dose with a p value of 0.0445, (b) (4)

Figure 2: Median change from baseline in number of urinary incontinence episodes per week during 12-week double blind treatment periods (mITT population). Source: Study report 20070060 page 69



Sensitivity analysis using the “per protocol” population (by the Sponsor) and the completer population (by the medical officer) did not demonstrate a significant difference from placebo for the primary efficacy endpoint. However, analysis by the biostatistics Division using LOCF to impute missing data did demonstrate a significant effect at a p value of 0.0445 for the 84 mg/day dose. (b) (4)

[Redacted text block]

Reviewer's comment: *This single Phase 3 study demonstrated statistically significant results for the primary efficacy endpoint for the 84 mg/day dose only. Almost 90% of the reduction in weekly urinary incontinence episodes is attributable to placebo.*

Table 11: Mean change from baseline in weekly urinary incontinence episodes as compared to placebo (source - approved labeling for each product).

Drug	Difference from Placebo	p value
Ditropan XR	8.2	---
Detrol LA	4.8	---
Gelnique	3.5	p < 0.0001
(b) (4)		
Oxytrol (2)	5.6	p = 0.0137
Sanctura XR (1)	3.8	p = 0.0024
Sanctura XR (2)	5.1	p < 0.001
Toviaz (1)	7.5	p < 0.001
Toviaz (2)	9.9	p < 0.001
Anturol	1.9	p = 0.0333

*

(b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

There are two secondary efficacy endpoints traditionally accepted by the Division for the purposes of labeling; change in urinary frequency and volume of urine per void from baseline as compared to placebo. The sponsor adjusted for multiplicity by increasing alpha to 0.0125 (2-sided) for the two secondary endpoints.

During the study, there were significant reductions in median average daily urinary frequency in both the oxybutynin groups compared with the placebo group (Figure 3). At baseline, the mean and median average daily urinary frequencies were similar across all treatment groups; median values were 10.7 micturitions in the oxybutynin 84 mg group, (b) (4) and 10.5 micturitions in the placebo group. At end of study (Week 12), median reductions (improvement) from baseline in average daily urinary frequency were -2.7 (b) (4) micturitions experienced by patients in the oxybutynin 84 mg (b) (4), compared with -2.0 micturitions in the placebo group. In the analysis of the reduction from baseline at Week 12 in average daily urinary frequency (using the Rank Transformation on values) the least square mean difference between oxybutynin 84 mg and placebo (difference: -45.3, p = 0.0005; < 0.0125) was statistically significant, in favor of oxybutynin 84 mg.

(b) (4)

Figure 3: Median number of voids per day during 12-week double blind period (mITT population).
Source: Study report 20070060 page 72



During the study, there were significant increases in median urinary volume per void in both the oxybutynin groups compared with the placebo group (Figure 4). At baseline, the mean and median urinary volume per void was similar across all treatment groups; median values were 189 mL in the oxybutynin 84 mg group, (b) (4), and 183 mL in the placebo group. At Week 12, median increases (improvement) from baseline in urinary volume per void were 24.3 (b) (4) in the oxybutynin 84 mg (b) (4), compared with 5.4 mL in the placebo group. In the analysis of the increases from baseline at Week 12 in urinary volume per void (using Rank Transformation on values), the least square mean differences between oxybutynin 84 mg and placebo (difference: 43.9, $p = 0.0017$; < 0.0125) were statistically significant, in favor of oxybutynin. (b) (4)

(b) (4)

Figure 4: Median urinary volume per void during 12-week double blind period (mITT population).
Source: Study report 20070060 page 74



Reviewer's Comment: *The 84 mg was the only dose that demonstrated superiority to placebo for the secondary endpoints (urinary frequency and volume voided). This provides confirmatory evidence of efficacy for this product and dosage.*

6.1.6 Other Endpoints

Other efficacy endpoints assessed include:

- Patient perception of bladder condition (PPBC)
- Urinary urgency (frequency and severity)
- Incontinence Impact Questionnaire (IIQ)
- Patient global Impression of Improvement (GAQ)

The outcomes for all of the tertiary endpoints were quite similar. In general, the outcomes for the 84 mg dose were statistically superior to placebo and the 56 mg dose was not (Table 12). There was no significant difference from placebo for either dose when either unadjusted numbers or the per protocol population were studied.

Table 12: Results of tertiary efficacy endpoints for Study 20070060. * Change from baseline at end of study as compared to placebo arm.

		84 mg p-value*	(b) (4)
PPBC		(b) (4)	
Urgency	Frequency		
	Severity		
IIQ			
GAQ			

Reviewer’s comment: Sponsor performed sensitivity analysis using the “per protocol” population did not support the above findings. Moreover, there was no correction for multiplicity. These tertiary endpoints are all exploratory and will not be included in the labeling.

6.1.7 Subpopulations

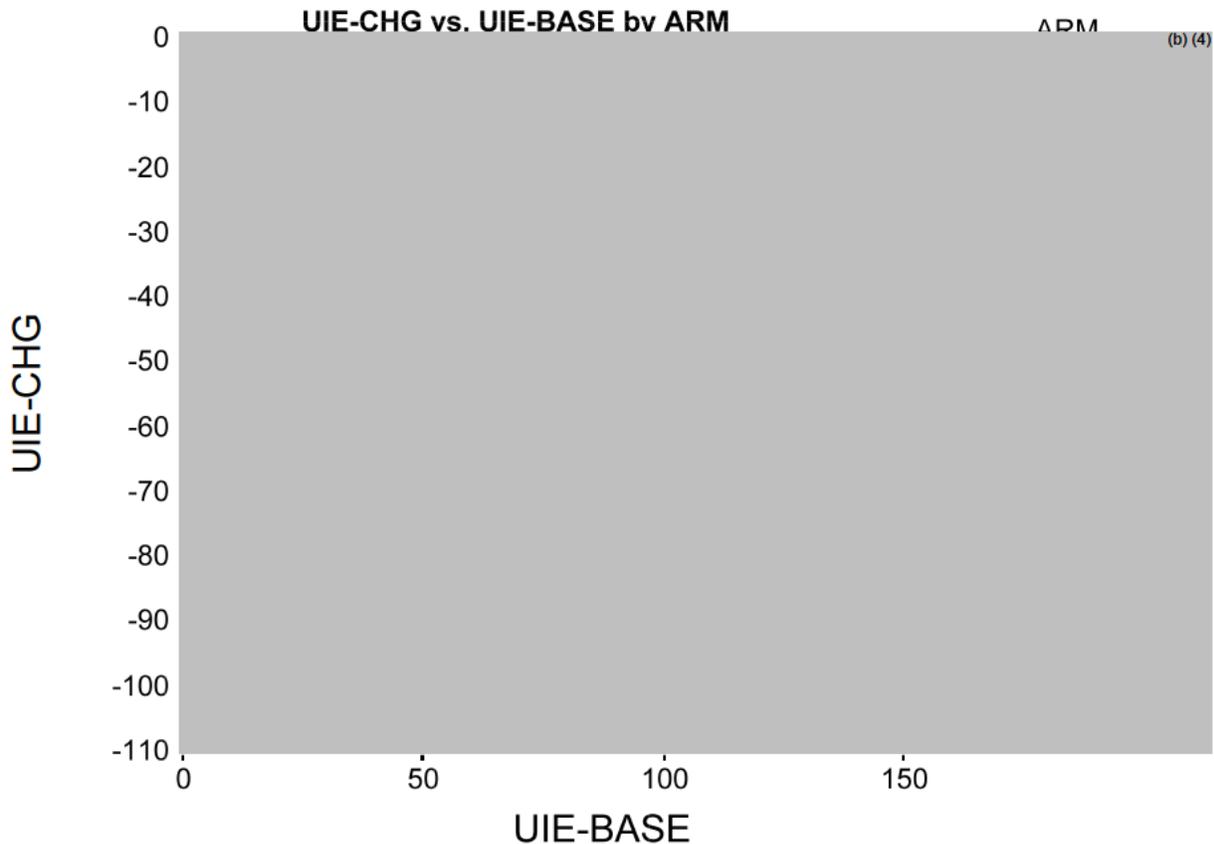
The following subset analyses of efficacy were performed by the medical officer:

- Age
- Gender
- Race
- BMI
- Baseline severity of symptoms
- Previous success with anticholinergics
- Formulation
- Preferred application site

There was no effect of age, gender, or race upon the primary efficacy parameter, change in urinary incontinence episodes per week from baseline as compared to placebo. The specific subset of women over 55 years of age was analyzed and there was no difference. BMI also did not have an effect upon the primary efficacy endpoint.

Baseline severity of symptoms ($p < 0.01$), incontinence episodes per week ($p < 0.0001$) and urinary frequency per day ($p = 0.0002$), did have an impact upon the primary endpoint, change in urinary incontinence episodes. Figure 5 shows the relationship between baseline urinary incontinence episodes (UIE-BASE) to the primary efficacy endpoint, change in urinary incontinence episodes (UIE-CHG). Note that placebo demonstrates greater efficacy (is lower) for the two extremes of the range of baseline severity of symptoms.

Figure 5: Effect of baseline severity of symptoms, urinary incontinence episodes at baseline (UIE-BASE), upon the primary efficacy endpoint of Study 20070060 (UIE-CHG) by study arm.



Subjects ($n = 65$) who had previously responded to other anticholinergic therapies for overactive bladder were included in this study and were represented in all three treatment groups. Their responses were no different from subjects that had never been treated with anticholinergic medications except in the placebo group where their response was significantly worse ($p = 0.01$). There was no difference in the outcomes based upon formulation used, [REDACTED] (b) (4). Finally, the preferred site of application had no effect upon outcome.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The (b) (4) 84 mg, demonstrated (b) (4) efficacy for the primary endpoint of reduction of urinary incontinence episodes at 12 weeks. (b) (4) the 84 mg dosage form demonstrated superiority for all of the secondary and exploratory tertiary efficacy endpoints. To be discussed later, the major adverse reaction, application site reactions, was not different when comparing the two doses studied. The typical anticholinergic side effects, dry mouth and constipation, was greater for the 84 mg dose but the cumulative incidence was not statistically different. Thus, the recommended dose for this medication from both an efficacy and safety perspective is 84 mg.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Overactive bladder is a chronic condition that potentially requires lifelong therapy. The duration of the primary efficacy trial was 12 weeks which is the same as that of all other approved products in the class. There was no evidence of tolerance during the twelve weeks, maximal treatment effect was obtained at approximately four weeks and was maintained for the duration of the study (Figure 2). The open label extension trial did not assess efficacy.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The following sources were reviewed for safety assessment:

1. Integrated summary of safety, including eight clinical studies. The safety review relies primarily on the findings of Study 20070060.
2. The 120-day Safety Update
3. Published literature and approved anticholinergic product labeling.

Five of the eight studies used the to-be-marketed formulation, (b) (4) including the majority of subjects in the Phase 3 study (20070060).

7.1.2 Categorization of Adverse Events

The sponsor categorized adverse events using MEDdra version 11.0.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The data were pooled as described above. However, the primary assessment of safety is derived from the double blind period of the single Phase 3 study: 20070060.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure was 639 subjects and 46,206.8 patient-days for all doses of 3% oxybutynin gel. The primary source for safety assessment is the double period of the single Phase 3 study, 20070060. The total exposure for the two doses, 56 mg and 84 mg, was 424 subjects with 31,657.8 patient day exposure (Table 13), accounting for almost 70% of the total exposure in drug development and the only part with placebo control.

Table 13: Summary of extent of exposure in the Phase 3 study and open label extension.

Study	Dose	Number of Subjects	Duration	Patient-Day Exposure
20070060	56 mg	210	12 weeks	15,351
	84 mg	214		16,306.8
Open label Extension	84 mg	77	24 weeks	12,089

The demographics and baseline characteristics for Study 20070060 and its open label extension (OLE) are shown in Table 14. The majority of subjects were post-menopausal white women, reflecting the underlying demographics of the OAB syndrome. Nevertheless, there was adequate representation of all ages, genders and race. The median BMI was 30 kg/m² (moderately obese) which is reflective of the population.

Table 14: Patient demographics and baseline characteristics for Study 20070060 and the open label extension (OLE). Source: ISS page 19.

Characteristic	Statistic	Oxybutynin 84 mg/day (N=214)	Oxybutynin 56 mg/day (N=210)	Placebo (N=202)	Overall (N=626)	OLE 84 mg/day (N=77)
Age (years)	Median	60	59	59	59	58
	Min, Max	24, 87	19, 89	21, 88	19, 89	32, 86

Gender, n (%)	Male	32 (15)	28 (13)	24 (12)	84 (13)	9 (12)
	Female	182 (85)	182 (87)	178 (88)	542 (87)	68 (88)
Race, n (%)	White	183 (86)	187 (89)	172 (85)	542 (87)	71 (92)
	Black	24 (11)	18 (9)	28 (14)	70 (11)	4 (5)
	Asian	1 (0.5)	2 (1)	2 (1)	5 (1)	1 (1)
	American Indian	0	1 (0.5)	0	1 (0.2)	0
	Other	6 (3)	2 (1)	0	8 (1)	1 (1)
BMI (kg/m ²)	Median	30	30	30	30	31
	Min, Max	17, 62	18, 52	19, 66	17, 66	20, 47

7.2.2 Explorations for Dose Response

The design of the single Phase 3 trial allowed for adequate evaluation of the effect of dose upon safety. Several doses were assessed during Phase 1 and 2 studies. However, these studies were very small and had short exposures. Moreover, they lacked placebo controls. In contrast, Study 20070060 utilized two doses, 56 mg and 84 mg, as well as a placebo control arm.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events in subjects in the Phase 1 and 2 studies. There were a total of nine subjects that experienced at least one serious adverse event in the single Phase 3 study. Serious adverse events in the two treatment arms were chest pain, fibula fracture, meniscus lesion, pneumonia, missed abortion, hepatic neoplasm, angina pectoris and abdominal pain. None of them were thought to be related to the study drug.

Reviewer's comment: *I reviewed all of the case narratives for these subjects and agree with the sponsor's conclusions.*

7.3.3 Dropouts and/or Discontinuations

There were no dropouts due to adverse events in the Phase 1 and 2 studies. In the Phase 3 trial there were 50 subjects (8%) that discontinued study drug due to treatment emergent adverse events, 5% in the placebo arm and approximately 10% in each treatment arm. The most common cause was application site conditions, which accounted for one third of the dropouts due to adverse events, followed by gastrointestinal and nervous system disorders. All of these adverse events were reported to be resolved.

7.3.4 Significant Adverse Events

There were no significant new adverse reactions reported with this drug product.

7.3.5 Submission Specific Primary Safety Concerns

There are currently numerous approved oxybutynin products on the market, including both oral and topical, with a well established safety profile. The primary safety concerns for a topical oxybutynin product include anticholinergic side effects, such as dry mouth and constipation, application site reactions, and increased urinary retention or elevated post void residual.

Anticholinergic side effects

The most common side effects related to the anti-muscarinic effect of this class of medications are dry mouth, constipation, blurred vision, urinary retention, and UTI. Table 15 shows the number and percent of subjects reporting anticholinergic adverse reactions in Study 20070060. The final row tabulates the number of subjects experiencing one or more of these adverse reactions demonstrating a dose response. Moreover, there was a significant difference between the 84 mg dose and placebo ($p < 0.05$).

Table 15: Anticholinergic adverse reactions reported for subjects in Study 20070060. Medical officer analysis

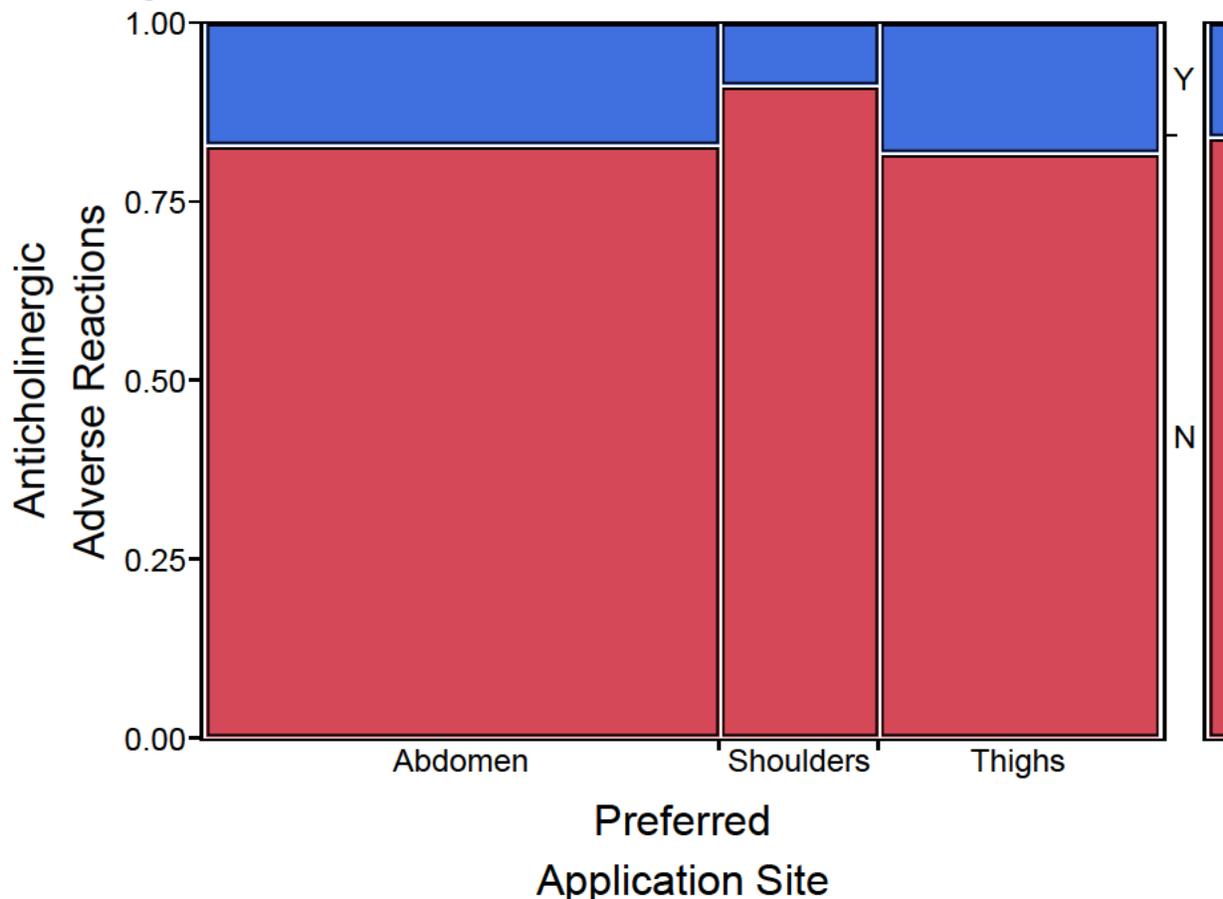
	Oxybutynin 84 mg (n=214)	Oxybutynin 56 mg (N=210)	Placebo (N=202)
Dry mouth	26 (12.1)	23 (11)	10 (5)
Constipation	8 (3.7)	3 (1.4)	5 (2.5)
Blurred vision	4 (1.9)	3 (1.4)	0 (0)
Urinary retention	0 (0)	0 (0)	3 (1.5)

UTI	6 (2.8)	9 (4.3)	4 (2)
Any	37 (17.3)*	29 (13.8)	21 (10.4)

* p < 0.05 as compared to placebo

Anticholinergic adverse reactions such as dry mouth and constipation are likely related to the extent of exposure to oxybutynin and its primary metabolite. There was no way to determine whether common anticholinergic adverse reactions, including dry mouth and constipation, were linked to exposure since pharmacokinetic sampling was not performed in the Phase 3 trial. In the preliminary site of application pharmacokinetic study (OXBTN/2006/223) it was shown that there was greater exposure when the gel was applied to the upper arms or shoulders. Analysis of the frequency of anticholinergic adverse reactions by preferred application site did not reveal any relationship (p=0.15). In fact, the subjects with shoulders as the preferred site had the lowest rate of anticholinergic adverse reactions (Figure 6). Combining the two active treatment arms, there were 224 subjects who utilized the abdomen, 69 subjects utilized the shoulders, and 121 preferred the thighs for their daily application. The rate of anticholinergic adverse reactions, including dry mouth, constipation, and urinary tract infection, were 17%, 9% and 18%, respectively.

Figure 6: Incidence of anticholinergic adverse reactions by preferred application site. Medical officer analysis.



Application site reactions

The sponsor broke down the various application site reactions into the following categories; erythema, rash, pruritus, irritation, and reaction. All subtypes of application site reactions were numerically higher for drug than placebo (Table 16). The percentage of subjects experiencing at least one form of application reaction was roughly equivalent amongst the two doses. Despite the lack of standards for recording or reporting application site reactions, the number of subjects with application site reactions of any kind were significantly more common for active drug (both dosages combined) than placebo ($p < 0.0008$).

Table 16: Application site adverse reactions reported for subjects in Study 20070060 reported as events (* reported as subjects). Medical officer analysis

	Oxybutynin 84 mg (n=214)	Oxybutynin 56 mg (N=210)	Placebo (N=202)
Erythema	8 (3.7)	8 (3.8)	3 (1.5)

Rash	8 (3.7)	9 (4.3)	1 (0.5)
Pruritus	6 (2.8)	3 (1.4)	1 (0.5)
Irritation	2 (1)	1 (0.5)	0 (0)
Reaction	3 (1.4)	5 (2.4)	0 (0)
Other	2 (1)	3 (1.4)	2 (1)
Any	24 (11.2)	22 (10.5)	6 (3.0)

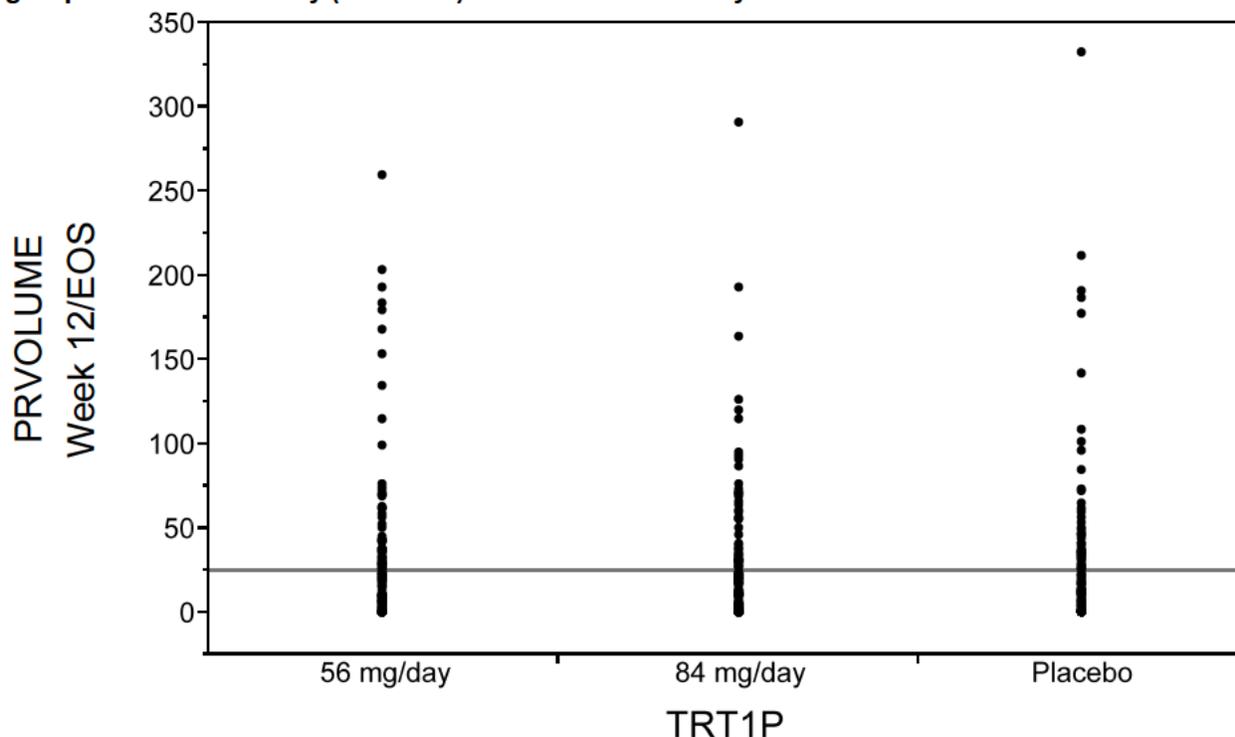
Analysis of the effect of the change of formulation (b) (4) upon the rate of application site reaction showed a significant association. The incidence of application site reactions of any type was 0% for the subjects receiving the original formulation (b) (4) of the active drug as compared to 13.7% in 335 subjects receiving the to-be-marketed formulation (b) (4) of the active drug ($p < 0.0002$).

Reviewer's comment: Application site reactions of any type were generally mild to moderate in degree and the overall incidence is comparable to other topical products already on the market. The product labeling will reflect the incidence of application site reactions reported with the to-be-marketed formulation.

Post void residual urine

Post void residual was measured at baseline and at the end of study (12 weeks) according to the protocol for all subjects. There was considerable missing data for this parameter. For instance, PVR data was available for only 494 subjects (79%) at baseline. The mean and median PVR were 21 cc and 10 cc, respectively. There was no significant change at the end of study and the treatment groups were the same as placebo (Figure 7)

Figure 7: There was no difference in the postvoid residual measurements (cc) in each treatment group at the end of study (12 weeks). Medical officer analysis



7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most common adverse reactions in the double-blind Phase 3 study were dry mouth (12%), application site erythema (3.7%), constipation (3.7%), application site rash (3.3%), application site pruritus (2.8%), urinary tract infection (2.8%), headache (2.8%), upper respiratory tract infection (2.8%) and nasopharyngitis (2.34%) of subjects receiving 84 mg per day (n=214). Table 17 lists those adverse reactions that occurred in more than 2% of the subjects receiving 84 mg/day and were also greater in proportion than the placebo arm.

Table 17: Common adverse reactions in the randomized, double-blind, placebo-controlled 12-week study (20070060) ($\geq 2\%$ and $>$ placebo). Medical officer analysis.

Adverse Event	Oxybutynin Gel 3% 84 mg/day			Placebo		
	Events	Subjects	%	Events	Subjects	%
Dry mouth	26	26	12.15	10	10	4.95
Application Site	29	24	11.2	6	6	3
Eye disorders	10	10	4.67	8	7	3.47

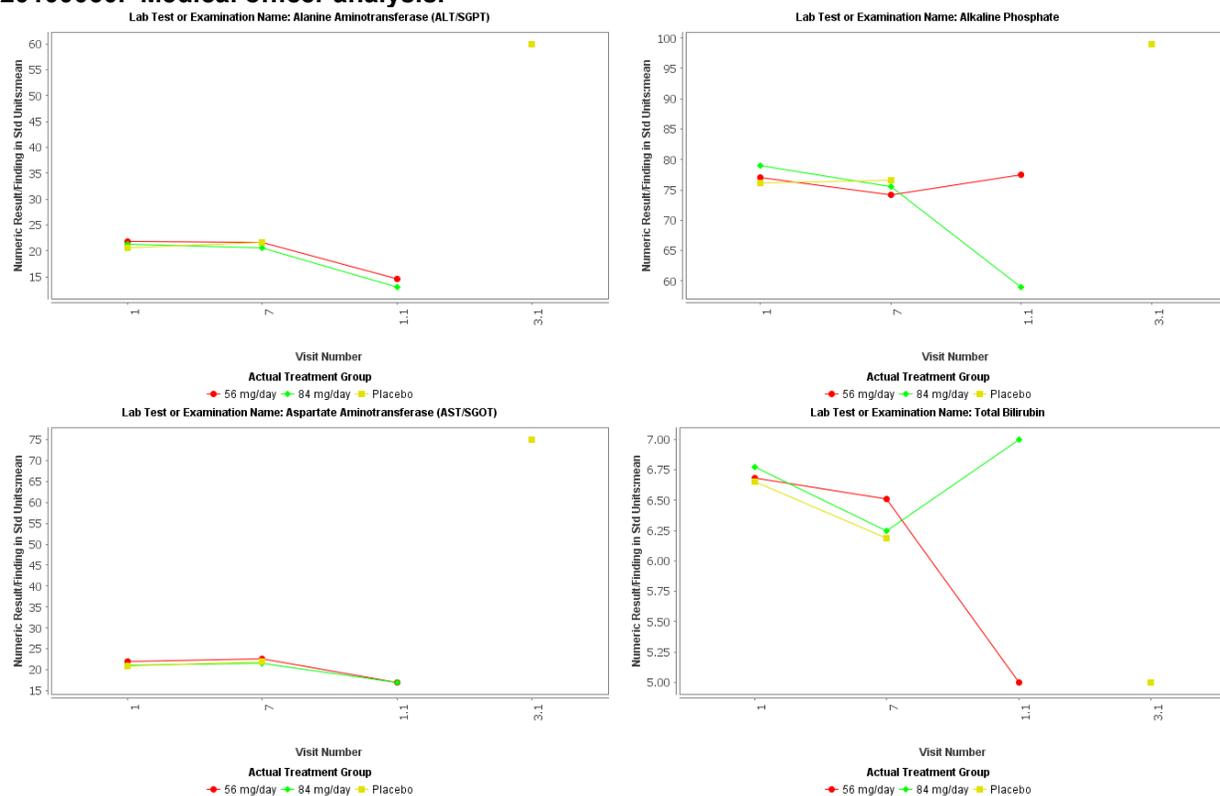
Clinical Review
Jonathan P Jarow
NDA # 202-513
Anturol - Oxybutynin Gel 3%

Constipation	8	8	3.74	5	5	2.48
Urinary tract infection	8	6	2.8	4	4	1.98
Nasopharyngitis	6	5	2.34	0	0	0

7.4.2 Laboratory Findings

There were no significant treatment-related adverse changes in laboratory safety parameters. Mean values for hematology and biochemistry variables remained within respective normal ranges throughout. Figure 8 shows the results for liver function tests throughout the placebo-controlled study and that the treatment groups track similarly. Shifts from normal at baseline to either below or above normal the reference range of the central laboratory during the course of the placebo-controlled study occurred in 5% of subjects. The most common shifts in the hematology labs were hematocrit, percent monocytes, and percent neutrophils. The most common shifts in biochemistry labs were glucose and uric acid. There were no obvious trends in regard to differences in chemistry values between treatment groups.

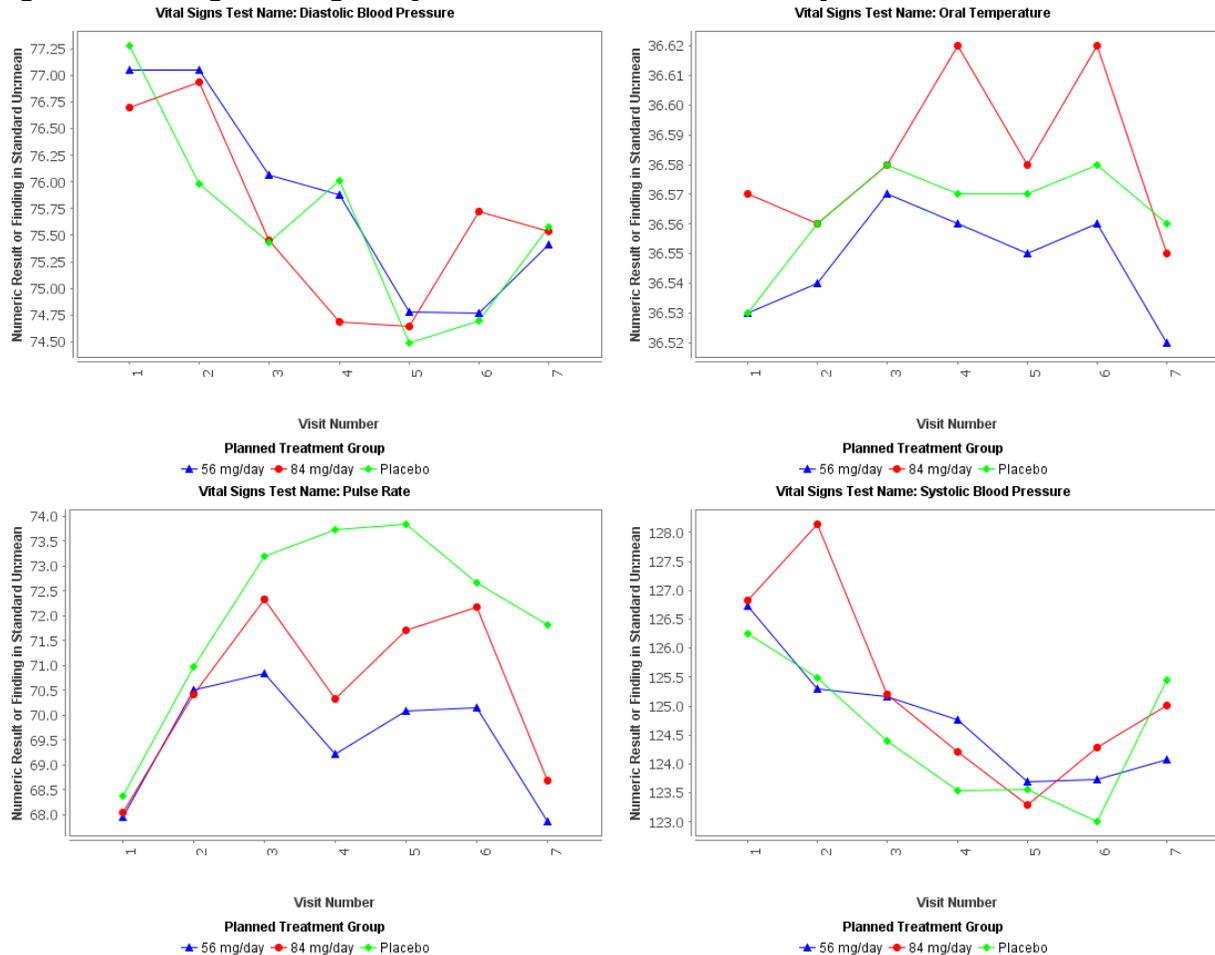
Figure 8: Mean liver function test laboratory result by Visit Number and treatment group in Study 20100060. Medical officer analysis.



7.4.3 Vital Signs

Vital signs were measured at each visit in Study 20070060. There was no effect of either dose of oxybutynin gel 3% on vital signs as compared to placebo during the course of the study (Figure 9).

Figure 9: Vital signs during Study 20070060. Medical officer analysis



7.4.4 Electrocardiograms (ECGs)

At baseline (Screening) 407 patients (65.0%) overall had ECG values within normal limits while 183 patients (29.2%) overall reported abnormal results which were considered not clinically significant. At the end of study (Week 12), 58.3% of patients overall had ECG values within normal limits and 28.9% of patients overall were reported for abnormal values which were considered not clinically significant. Only 1 patient (oxybutynin 56 mg) was reported for clinically significantly abnormal ECG results at

Week 12. For a small proportion of patients (9.1% overall) ECG readings worsened at Week 12 compared with baseline.

There were no differences in the proportion of patients across treatment groups with normal or abnormal ECG values and no obvious trends were observed. Normal (at baseline) to abnormal (at Week 12) shifts considered not clinically significant were recorded for 51 patients (8.1%) overall, with no differences observed between treatment groups. Only one patient (in the oxybutynin 56 mg group) had an abnormal, not clinically significant ECG value at baseline with a clinically significant shift at Week 12. The abnormal finding was reported as first degree atrioventricular block.

Reviewer's comment: *The availability of safety data for other oxybutynin products has not raised any questions about oxybutynin use causing significant changes in ECG parameters. Therefore, no further evaluation of the effects of oxybutynin gel on ECGs are warranted.*

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Not assessed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

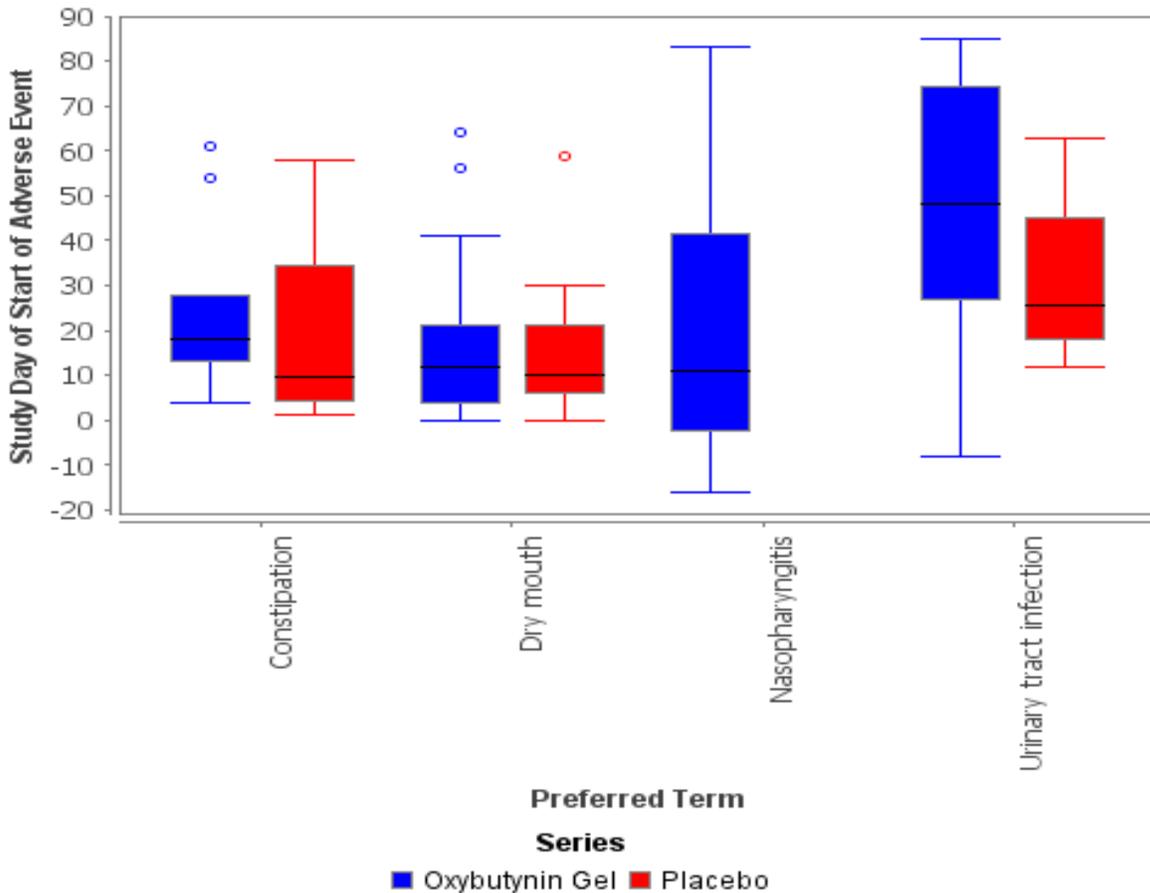
There was a dose relationship of some of the anticholinergic related adverse reactions such as constipation and dry mouth. There did not appear to be a dose dependency for application site reactions, urinary tract infections or nasopharyngitis. Further exploration of the lower dose is not necessary from a safety perspective because none of the dose dependent effects identified were different from those reported in the safety profiles of other approved oxybutynin products

7.5.2 Time Dependency for Adverse Events

Time dependency for adverse events was not studied by the sponsor. Examination of the submitted data did not reveal any patterns to the onset or duration of any of the adverse events reported in the double-blind, 12-week duration phase 3 study. Figure 10 shows the box plots for the time of onset for each of the common adverse reactions excluding application site reactions. The median time of onset for dry mouth and constipation was approximately 2 to 4 weeks, whereas, urinary tract infection was 8 weeks. The median time of onset for application site reactions was also 2 to 4 weeks in

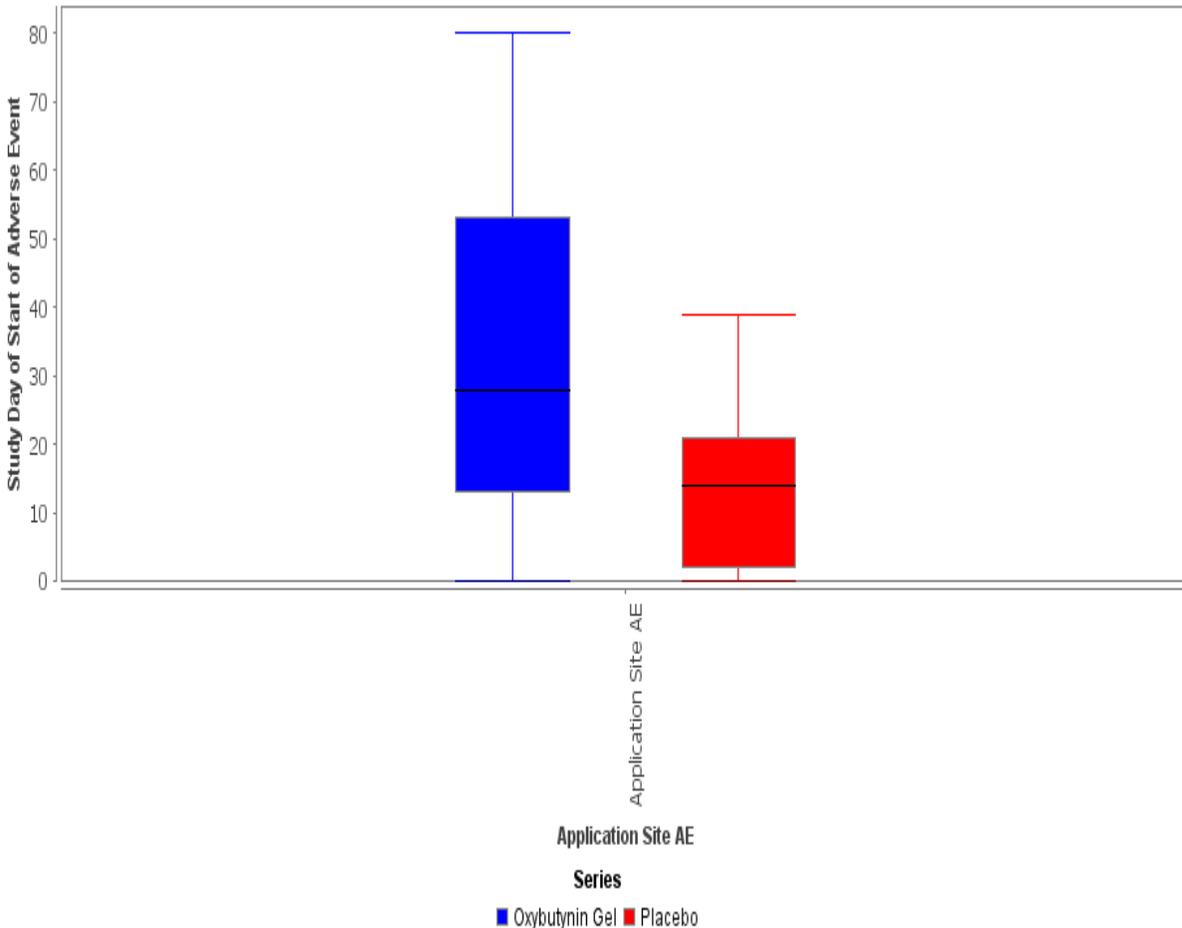
a separate analysis (Figure 11). Only two additional subjects experienced application site reactions in the open label extension and neither of these two discontinued the medication because of it.

Figure 10: Time of onset, relative to randomization, of common adverse reactions by treatment arm in Study 20100060. Medical officer analysis.



Using Recoded Planned Treatment Group - ADSL3.SOURCE
 =PhaseForward AND ADSL3.Safety Population Flag =Y

Figure 11: Time of onset of all application site adverse reactions relative to randomization in Study 2010060. Medical officer analysis.



Time of Onset of Application Site AE (Recoded Adverse Events Preferred Terms containing 'Application site') AE BY
Recoded Planned Treatment Group (Recoded Planned Treatment)

7.5.3 Drug-Demographic Interactions

Race, Age, Gender and BMI

There was no observed difference in the rates of various adverse events based upon race, age, gender or BMI. The specific issue of application site reactions in the elderly was assessed. The mean age and range for those subjects with application site reactions was the same as those without.

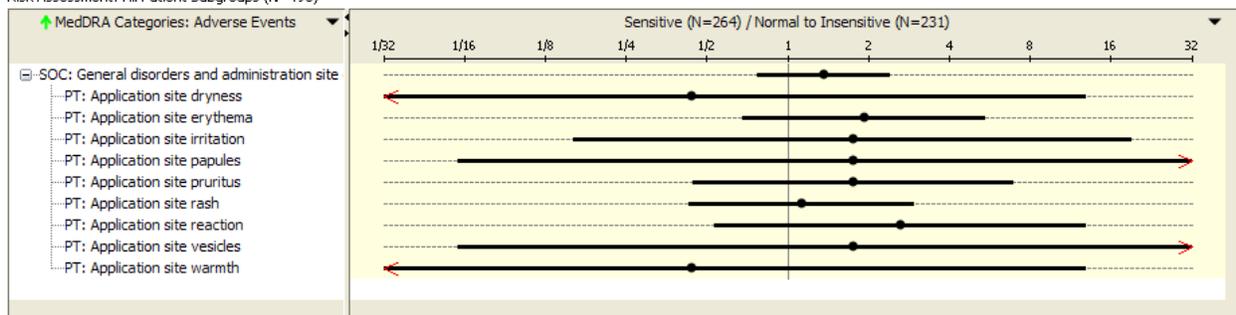
Skin Type

Subjects' skin type was categorized upon entry into the study on a six point scale from extremely sensitive skin that never tans to insensitive skin that never burns. The rate of

application site reactions were significantly higher for subjects with sensitive skin (16%) as compared to subjects with normal or insensitive skin (9%) (p=0.03). Figure 12 shows the relative risk for any and each type of application site reaction for subjects with sensitive skin using normal or insensitive skin as a reference.

Figure 12: Relative risk of all application site reactions (General disorders) and each individual type of reaction comparing skin types: sensitive to normal or insensitive. Medical officer analysis.

Risk Assessment: All Patient Subgroups (N=496)



(b) (4)

7.5.4 Drug-Disease Interactions

Not studied.

7.5.5 Drug-Drug Interactions

None studied.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

From Ditropan Labeling: 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

7.6.2 Human Reproduction and Pregnancy Data

From Ditropan Labeling:
Pregnancy Category B.

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

The safety of Oxybutynin 3% administration to women who are or who may become pregnant has not been established. Therefore, Oxybutynin 3% should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

7.6.3 Pediatrics and Assessments

Safety and effectiveness of Oxybutynin gel 3% in pediatric patients have not been established to date.

The safety and efficacy of oral oxybutynin were studied in 30 children in a 24week, open-label trial. Patients were aged 5-15 years, all had symptoms of detrusor overactivity in association with a neurological condition (e.g., spina bifida), all used clean intermittent catheterization, and all were current users of oxybutynin chloride. Study results demonstrated that the administration of oral oxybutynin was associated with improvement in clinical and urodynamic parameters.

At total daily doses ranging from 5 mg to 15 mg, treatment with oral oxybutynin was associated with an increase from baseline in mean urine volume per catheterization from 122 mL to 145 mL, an increase from baseline in mean urine volume after morning awakening from 148 mL to 168 mL, and an increase from baseline in the mean percentage of catheterizations without a leaking episode from 43% to 61%. Urodynamic results in these patients were consistent with the clinical results. Treatment with oral oxybutynin was associated with an increase from baseline in maximum cystometric capacity from 230 mL to 279 mL, a decrease from baseline in mean detrusor pressure at maximum cystometric capacity from 36 cm H₂O to 33 cm H₂O, and a reduction in the percentage of patients demonstrating uninhibited detrusor contractions (of at least 15 cm H₂O) from 39% to 20%.

As there is insufficient clinical data for pediatric populations under age 5, oral oxybutynin is not recommended for this age group.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The information on overdosage that was selected for labeling is standard across the class. The text for labeling will include the following:

Overdosage with oxybutynin has been associated with anticholinergic effects including central nervous system excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, exhaustion, heat sensitivity, and urinary retention. Oral ingestion of 100 mg oxybutynin chloride in association with alcohol has been reported in a 13-year-old boy who experienced memory loss, and in a 34-year-old woman who developed stupor, followed by disorientation and agitation on awakening, dilated pupils, dry skin, cardiac arrhythmia, and retention of urine. Both patients recovered fully with symptomatic treatment. If overexposure occurs, monitor patients until symptoms resolve.

Reviewer's comment: *There is no reason to believe at this time that overdosage with Anturol will be significantly different from other oxybutynin products.*

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

This product is not approved in any other country, so no postmarketing data is available for review.

9 Appendices

9.2 Labeling Recommendations

The proposed labeling submitted by the Sponsor was reviewed and the following major suggested changes were accepted by the Sponsor:

- (b) (4)
- Addition of angioedema to Warnings and Precautions
- Addition of a statement regarding the overall incidence of application site reactions of any type using the to-be-marketed formulation in the Adverse Reactions section.
- Changes to the pharmacokinetic graph.
- Wording changes to the Clinical Studies section.
- Additions to Patient Counseling section.

9.3 Advisory Committee Meeting

An advisory committee meeting was not held because this product is not a new molecular entity and there are no unresolved safety or efficacy issues.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JONATHAN P JAROW
12/06/2011

SURESH KAUL
12/06/2011

NDA 202513

Medical Officer's 45-Day Filing Memorandum

Application Letter Date: February 8, 2011
45-Day Filing Review Date: April 9, 2011
PDUFA Goal Date: December 8, 2011

Related Submissions: IND 070527
NDA 202513 (Gelnique)
NDA 21-351 (Oxytrol TDS)

Product, route and dose: 3% 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 202513 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 3 study of efficacy and safety (20070060), 6 phase 1 studies, one Phase 2 study, the draft label, and financial disclosures for investigators of Study 20070060, NDA 202513 is fileable from a clinical perspective.

II. Background

Brief Regulatory History:

Oxybutynin 3% Gel (OX 3%) is an anticholinergic product developed by Antares Pharma, 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 proprietary name, Anturool, has been reviewed by the Division of Medication Error Prevention and Analysis and found acceptable. The proposed formulation is a metered pump dispensing approximately 1 ml (28 mg) per pump actuation. The proposed dose is (b) (4) three pumps of Anturool applied once daily to clean, dry intact skin on abdomen, upper arms/shoulders, or thighs. There is no specific guidance on starting dose selection or dose adjustments for specific populations. OX 3% has not been approved for marketing in any country.

The sponsor opened IND 070527 in March, 2005. An End-of-Phase 2 meeting was held with the sponsor in May, 2006, during which the Division "recommended" two phase 3 studies to provide sufficient evidence of safety and efficacy for approval. In lieu of that, the Division recommended a single study with "conclusive" results defined as being both statistically and clinically significant. Clinical significance would be a review issue. The Division recommended that at least 50 subjects complete 6 months of exposure to the drug product.

An SPA was submitted in August of 2006 for the Phase 3 trial. The Division recommended some changes and a formal agreement was never reached. Trace levels of (b) (4) was discovered in the drug product during the phase 3 trial. The drug product was altered (b) (4) and the sponsor performed a bridging study between the two formulations.

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 seven clinical pharmacology studies and one phase 3 safety and efficacy trial (see Table 1).

Table 1: Summary of clinical studies with OX 3%

Type of Study	Objective	Oxybutynin Gel 3% Daily Dose	Formulation	Duration of Rx	# of Subjects (M/F)	Age Range (years)
Phase 1					Healthy Subjects	
OXPK2 (SCO 5157)	Pilot PK	2 g (60 mg) 1 g (30 mg)	(b) (4)	7 doses	8 (0/8)	27-47
OXBTN/2006223	Application site	2.8 g (84 mg)	(b) (4)	3 doses	30 (6/24)	18-42
SCO 5432	Bioequivalence	2.8 g (84 mg)	(b) (4)	14 days	58 (26/32)	22-52
SCO 5488	Effect of Showering	2.8 g (84 mg)	(b) (4)	19 days	22 (13/9)	21-53
SCO 5486	Transfer potential	2.8 g (84 mg)	(b) (4)	2 doses	28 (14 treated) (5/9)	24-52
SCO 5487	Sunscreen	2.8 g (84 mg)	(b) (4)	3 doses	20 (6/14)	20-51
Phase 2					Healthy Subjects	
1034-PhII	Dose-ranging PK	1.4 g (42 mg) 2 g (60 mg) 2.8 g (84 mg)	(b) (4)	20 days	48 (12/36)	19-53
Phase 3					OAB Subjects	
20070060	Efficacy/Safety	Placebo 1.9 g(56 mg) 2.8 g (84 mg)	(b) (4)	12 weeks	626 (84/542)	19-89

20070060 OLE*	Open-label Extension	2.8 g (84 mg)	(b) (4)	24 weeks	78	
---------------	----------------------	---------------	---------	----------	----	--

*Study has been completed but not yet submitted
Source: Synopses of Individual Studies, Module 2.7.6

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

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 NDA submission contains a single well controlled Phase 3 trial (Study 20070060) and a confirmatory pharmacokinetic study (Study 1034-PhII), required by the Division at the end of Phase 2. The study design and endpoints were agreed upon during these same discussions.

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 20070060 was a large, multicenter study. Although concentration-response for oxybutynin and its metabolite, desethyloxybutynin, is not well characterized, the pharmacokinetic of OX 3% appears to be similar to that of an approved oxybutynin 10% gel. Taken all together, a single confirmatory study should provide sufficient evidence to support filing of this NDA.*

Table 3: Disposition of subjects in Study 20070060.

	Oxybutynin 3% Gel		Placebo
	84 mg	56 mg	
Randomized	214	210	202
Completed	177	165	151
Terminated early	37	45	51
Open-label extension	30	31	25

Table 4: Daily urinary incontinence episodes at baseline and change from baseline to Endpoint (mITT)

Daily urinary incontinence episodes	Statistics	Placebo	OX 3% 56 mg/day	OX 3% 84 mg/day
N			147	
Baseline	Mean (SD) Median	45.8 (29) 42	50 (32) 47	43.6 (28) 37.3
Endpoint change from baseline	Mean (SD) Median	-20 (27) -16.3	-24.8 (29) -21	-21.9 (25) -18.7

Reviewer's comment: The magnitude of treatment effect of OX 3% appears modest (mean treatment difference 4.7/week). This treatment effect, however, is more or less similar to those observed with some other approved medical treatments of OAB (see Table 4).

Table 5: Treatment effect of other OAB products

Products	Placebo	Drug	Comments
Gelnique 10% #incontinence episodes <u>per day</u>			<i>Treatment difference: -3.5 episodes/week</i>
Mean (SD) Baseline	5.4 (3.28)	5.4 (3.26)	
Mean (SD) change from baseline	-2.5 (3.06)	-3.0 (2.73)	
Oxytrol TDS #incontinence episodes <u>per day</u>			<i>Treatment difference: -5.6 episodes/week</i>
Mean (SD) Baseline	5.0 (3.2)	4.7 (2.9)	
Mean (SD) change from baseline	-2.1 (3.0)	-2.9 (3.0)	
Detrol LA- # incontinence episodes <u>per week</u>			<i>Treatment difference: -4.8 episodes/week</i>
Mean Baseline	23.3	22.1	
Mean change from baseline	-6.9	-11.8	

Source: Gelnique NDA, Oxytrol TDS, Detrol LA product labeling

Preliminary efficacy conclusions

- After a preliminary review, treatment with OX 3% appears to result in a statistically significant reduction 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 OX 3% 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:

- total patient exposure at relevant doses that is clearly inadequate to evaluate safety*
- 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*
- absence of a comprehensive analysis of safety data*
- absence of an analysis of data supporting the proposed dose and dose interval*

Response: No.

Safety Exposure

In total, the NDA contains safety data from 649 subjects with 34,417 patient days of exposure to OX 3%. This includes 449 OAB patients in the integrated phase 3 study (double blind and open-label) and 200 healthy subjects in the phase 1 and 2 studies. There was additional exposure in 77 of the original OAB subjects evaluated in an open-label extension of the Phase 3 study. The new formulation (to be marketed) was used in five of these studies including approximately 75% of the subjects in the Phase 3 study. There were 672 treatment-emergent adverse effects (TEAE) in 52% of the intent to treat population in the Phase 3 study (Study 20070060). Nine subjects had a serious adverse event and none were thought to be related to the study drug. There were no deaths. Fifty subjects discontinued the study drug due to a TEAE. The adverse events of interest by dose are listed in Table 6. There were no clinically significant trends in laboratory changes by dose. Moreover, there were no significant trends for ECG changes.

Table 6. Treatment-emergent adverse events experience in the Phase 3 study.

	Oxybutynin 84 mg/day (N=214)	Oxybutynin 56 mg/day (N=210)	Placebo (N=202)
Patients ≥ 1 TEAE	114 (53)	120 (57)	91 (45)*
GI	40 (19)	41 (20)	22 (11)*
Dry Mouth	26 (12)	23(11)	10 (5)*
Constipation	8 (4)	3 (1)	5 (3)
Administrative site	24 (11)	25 (12)	4 (2)*
Respiratory	12 (6)	13 (6)	10 (5)
Migraine	0 (0)	0 (0)	3 (2)*
Eye Disorders	10 (5)	7 (3)	5 (3)
Urinary Retention	0 (0)	0 (0)	3 (2)*

Reviewer's comments:

1. Preliminary review of the case narratives for the nine serious adverse events confirms the sponsor's conclusion that they were not treatment-related.
2. Although the 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 described in this NDA is adequate to evaluate skin safety.
3. Overall, the quantity and duration of patient exposure was adequate.

Person-to-person transfer: The potential for dermal transfer of oxybutynin from a treated person to an untreated person was evaluated in Study SCO 5486. The untreated partners not protected by clothing had detectable plasma concentrations of oxybutynin (mean C_{max} = 0.656 ng/mL). This represents approximately 20% of the exposure for treated subject. There was essentially zero transfer via dressed skin contact.

Reviewer's comment: Transfer of oxybutynin to a partner via close contact can be adequately addressed in the product label.

Preliminary safety and tolerability conclusions

- The safety profile of Oxybutynin 3% 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.
- Compared to placebo, OTG treatment was not associated with an excess of serious adverse events, hematologic, CNS, or renal adverse events.
- Patient exposure to OTG is acceptable.
- No additional formal risk management program (RMP) activities are recommended at this time.

3. Other considerations of Filing Review

Review of Financial Disclosure Documents

Form FDA 3454 dated December 17, 2010 signed by Kaushik J. Dave, RPh, PhD, MBA, Senior Vice President Product Development, Antares Pharma, Inc, was submitted. Financial disclosure documents were submitted only for clinical investigators (principal and sub-investigators) for Study 20070060; this approach is acceptable, because the approval of this NDA will be based primarily on this study.

Labeling

The proposed labeling 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 3% and previously approved oxybutynin products. The proposed draft labeling was submitted as a Adobe acrobat and Word document file.

Pediatric Review Committee (PeRC): The request for waiver of pediatric studies should be forwarded to PeRC for review and comments.

Pediatric Waiver: The sponsor requested a waiver for conducting pediatric studies in children (b)(4) under 21 CFR 314.55(c)(2)(i). This reviewer recommends granting this request pending evaluation by PeRC.

Division of Scientific Investigations (DSI) Audit: A routine DSI audit is not recommended. Study 20070060 is the only confirmatory study supporting the efficacy and safety of this product. However, review of the safety and efficacy by site does not reveal that there will be any effect upon the outcome of a limited routine DSI audit of 2 or 3 large U.S. study sites. This audit issue will be further discussed at the filing meeting.

4 Summary of Initial Clinical Review

Efficacy:

1. A preliminary review of the efficacy data suggests the oxybutynin gel 3% has efficacy for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency when analyzed using imputation of missing data. The statistical analysis will be a review issue as well as whether the level of efficacy clinically meaningful.

Safety:

2. After a preliminary evaluation, the safety profile appears to be similar to that of other anticholinergic products approved for the treatment of OAB.
3. Skin safety, especially skin sensitization, will be a review issue.

Others:

4. Review of the submitted financial disclosure did not reveal conflict of interest.
5. The format of the proposed label complies with the Physician Labeling Rule (PLR).
6. Consults will be requested from the following: PeRC, DDMAC, DMEPA, and DRISK

Conclusion: From a clinical perspective, this NDA is fileable.

Jonathan P Jarow, M.D.
Medical Officer
Division of Reproductive and Urologic Products

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
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	
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 arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
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			
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 adverse dropouts (and serious adverse events if requested by the Division)?	X			

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
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 (<i>e.g.</i> , 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			
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 clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jonathan P Jarow
Reviewing Medical Officer

4/4/2011
Date

Suresh Kaul
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/

JONATHAN P JAROW
04/04/2011

SURESH KAUL
04/04/2011