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RESEARCH**

APPLICATION NUMBER:
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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 6, 2011
From	Suresh Kaul, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA#	202-513 Original 1 (b) (4)
Applicant	Antares Pharma, Inc
Date of Submission	February 8, 2011
PDUFA Goal Date	December 8, 2011
Early Action Date	December 7, 2011
Proprietary Name / Established (USAN) names	Anturol Oxybutynin Chloride 3% Gel
Dosage forms / Strength	3 pumps once daily (84 mg) (b) (4)
Proposed Indication(s)	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Recommended:	<i>Approval of 84 mg dose</i> (b) (4)

1. Introduction

I believe that ANTUROL (oxybutynin gel 3%) should receive an **approval action for the indication “to treat overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.”** The recommended dose is 84 mg once daily applied as gel. Oxybutynin gel 3% (84 mg) did demonstrate statistically significant (p value = 0.0445) efficacy for its primary endpoint. Statistically significant improvements in secondary end points i.e., daily urinary frequency (p=0.0010) and urinary void volume (p<0.0001) were also seen with 84mg ANTUROL relative to placebo.



(b) (4)

No significant safety issues for either dose (56 mg or 84 mg) were detected.

2. Background

Overactive bladder (OAB) as defined by the International Continence Society is 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.

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, botulinum toxin injection of the detrusor (in patients with MS and SPI) and bladder surgery.

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.

Oral antimuscarinic agents produce adverse reactions resulting from 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). Anticholinergic side effects continue to be a major cause of patient noncompliance and treatment discontinuation.

Transdermal formulations of oxybutynin (TDS) were 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. However, transdermal formulations produce application site reactions and these are the most frequently reported adverse reactions and also a common reason for treatment discontinuation.

Regulatory Background:

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 suggestion 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 an increased sample size.

An End of Phase 2 (EOP2) 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.” 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.

A special protocol assessment (SPA) 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 patient 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 and placebo groups could be detected with 90% power.

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 C_{max}). Therefore, 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 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 desethyloxybutynin (DEO) following application of oxybutynin gel with available data on the pharmacokinetics of the oxybutynin transdermal patch (Oxytrol) and also oral extended release oxybutynin. These serum levels were comparable across oxybutynin products and, in my opinion, would constitute adequate supportive 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. Key proposed changes included 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 determined to be acceptable by the Statistical Team.

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

The Division also recommended that due to a change (b) (4) 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.

Currently Available Oxybutynin Chloride as an Active Ingredient

Oxybutynin chloride is currently available in immediate release (IR), extended release (ER), and transdermal formulations. The approval history of these products is as follows:

Oxybutynin chloride 5 mg tablet (Ditropan®) was the first oxybutynin product, approved in July, 1975. The product was approved for use in both adult and pediatric populations.

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.

Oxybutynin chloride 5, 10, and 15 mg extended release (Ditropan XL®) tablet 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.

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.

Oxybutynin chloride gel 10% (Gelnique®) was approved for use in adults in January 2009.

3. CMC/Device

From the Office of New Drug Quality Assessment, Division II, Branch IV, Bogdan Kurtyka, Ph.D and Donna Christner, Ph.D, the chemistry review team made the following recommendation:

Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

All facilities involved are in compliance with cGMP.

In addition, labels do have adequate information as required.

Therefore, from a CMC perspective, this NDA is recommended for approval in its present form.

Recommendation on Phase 4 (Post-Marketing) commitments

No CMC related Phase 4 commitments or requirements are proposed at this time.

CDTL Comment:

I concur with the CMC review and their recommendation for approval. All recommended labeling changes were incorporated into the draft label.

ONDQA (Biopharmaceutics) reviewer Tapash K. Gosh, Ph.D made the following determination during the review process:

On November 7, 2011, the Applicant accepted on an interim basis the Agency's recommended acceptance criteria for the *in vitro* drug Release Rate test using the following *in vitro* testing conditions:

 (b) (4)

The sponsor stated that above acceptance criteria for the *in vitro* "Release Rate Test" will be implemented on an "*interim basis*" for one year. The Applicant also agreed to collect and provide additional *in vitro* drug release rate data from at least ten (10) commercial batches of ANTUROL Gel 3% manufactured after approval date as a Post marketing Commitment. These data will be used to set the final regulatory acceptance criteria for the drug Release Rate test.

On November 9, 2011, sponsor was asked to submit an official document attesting the following:

The Agency proposed the interim specification of  (b) (4) for both release and stability after review of additional data dated November 4th, 2011, provided by the sponsor. Further, once ten (10) commercial batches are manufactured, the sponsor was asked to submit data so that a final specification can be set. Sponsor accepted the Agency's proposal on <DATE>.

Therefore, finished drug product specifications SPEC-QUA- 11-001, ANTUROL Finished

Drug Product Specification: 30 Metered Dose Unit and SPEC-QUA-11-002, ANTUROL Finished Drug Product Specification: 90 Metered Dose Unit have been updated accordingly to reflect the interim Release Rate: Slope specification range of (b) (4) as follows:

Table 1: Oxybutynin Gel 3% Finished Product Release and Stability Specifications, 100mL/45mL

Test	Method	Release Specification	Stability Specification
Release Rate (Diffusion Rate)			(b) (4)

Source: ONDQA Review

Recommendation:

ONDQA-Biopharmaceutics evaluated the information provided as of November 9, 2011, to support the approval of NDA 202-513 for Anturool (Oxybutynin) Gel 3%. From the Biopharmaceutics point of view the provided information/data was found satisfactory and NDA 202-513 is recommended for approval. No formal Post Marketing Commitment is needed.

CDTL Comment:

I concur with both CMC and ONDQA-Biopharmaceutics recommendation for approval.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Laurie McLeod-Flynn, PhD and Lynnda Reid PhD, had the following discussion of non-clinical findings and the recommendation in their final review.

Discussion

No pivotal nonclinical studies were submitted with this NDA. All necessary studies were submitted for the Reference Listed Drug, Ditropan (5 mg). Oxybutynin 3% gel has been shown to result in clinical exposures that are comparable to those of Ditropan.

Desethyloxybutynin (DEO), the pharmacologically active metabolite of oxybutynin, has a lower exposure level for oxybutynin 3 % gel than for Ditropan. Cyclohexylmandelic acid or CHMA, the inactive metabolite of oxybutynin, is present as an impurity in oxybutynin 3% gel, and will have a specification limit set at (b) (4)

Pharmacology-Toxicology Recommendation

There is no impediment to approval of this application from a Pharmacology/Toxicology perspective.

Additional Non Clinical Recommendations

None.

Recommended Labeling Changes:

Labeling recommendations from the Pharmacology/Toxicology review team were made to the following sections:

Carcinogenesis, Mutagenesis, Impairment of Fertility, Pregnancy, Nursing Mothers and Pediatric Use sections. All the recommendations were incorporated into the draft label.

CDTL Comment:

I concur with Pharm-Tox review team's recommendation for approval and labeling.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, Sayed Al Habet, RPh, PhD, and Myong Jin Kim, PharmD, made the following recommendation in their review:

Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant.

Post-Marketing Requirements / Commitments

From the Clinical Pharmacology perspective, **no** phase 4 commitment/requirement is applicable to this NDA.

CDTL Comment

I concur with Clinical Pharmacology review team's recommendations.

Summary of Important Clinical Pharmacology Findings:

In addition to the double blind placebo controlled safety and efficacy phase 3 study in approximately 600 patients at two doses of 56 mg and 84 mg for 12 weeks (Study # 2007/0060), the sponsor also conducted the following clinical pharmacology studies:

BE Results of the original Phase III and the to-be-marketed (TBM) Formulations

The bridging BE study was conducted at the highest dose (84 mg, 3 actuations) applied to the abdomen for 7 days (Study SCO 5432). This study used a crossover design in 58 healthy subjects with a washout period of 14 days between treatments. The 90% CI for C_{max} was 111.88-136.83 and for AUC was 106.28 and 126.45. Based on this, the two formulations failed to demonstrate BE (Table 2).

Table 2: 90% CI for PK Parameters (Study # SCO 5432)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{avg}	ANOVA	log	a/b	115.92	106.28	126.45	27.4
C _{max}	ANOVA	log	a/b	123.73	111.88	136.83	32.0
C _{min}	ANOVA	log	a/b	106.39	96.01	117.90	32.7
PTF	ANOVA	log	a/b	130.10	115.14	147.02	39.3
t _½	ANOVA	log	a/b	98.33	91.76	105.37	21.7
TC _{avg}	ANOVA	lin	a-b	-0.09	-0.73	0.54	18.8
T _{max}	Hauschke	Lin	a-b	-4.00	-6.00	-1.00	

The exposure following application of the TBM formulation (b) (4) was higher than that of the old formulation (b) (4). The mean (±SD) of AUC_(0-t) was 156 ± 32.7 and 139.0 ± 70.78 ng.h/mL and C_{max} was 9.7 ± 5.1 and 8.09 ± 4.94 ng/mL following the TBM and old formulations, respectively.

CDTL Comment:

It should be noted that during the Phase III trial the sponsor changed the formulation (b) (4)

At that time, 130 patients in Phase III were exposed to the old formulation (b) (4). The trial was continued with a new formulation (b) (4) in 496 patients.

Although, the two formulations were not BE, sponsor was allowed to pool the data collected from the results of both formulations (b) (4). This decision was made by the Clinical Pharmacology review team earlier during the drug development program since the exposure was only marginally higher for the TBM formulation. The Clinical –Pharmacology review team wrote the following in their review:

“It appears that this difference in formulations may not be clinically significant considering the long history of safety data from several products containing oxybutynin. Also, in Phase III studies, no unusual safety issues were observed from either formulation.”

Effect of Application Site

The effect of changing the application site (Study # OXBTN/2006/223) was conducted following a single dose of 84 mg oxybutynin gel in 25 healthy males and females in three way crossover design applied to three sites: site A (abdomen), site B (upper thighs) and site C (upper arms and shoulders).

The exposure was highest after application of the gel to arms and shoulders compared to abdomen and thighs. The mean (SD) C_{max} was 8.81 ± 5.49, 6.31 ± 3.53 and 5.80 ± 2.61 ng/mL and AUC was 329.05 ± 139.06, 284.09 ± 108.17 and 286.91 ± 145.25 ng.h/mL for the arms/shoulders, abdomen, and thighs, respectively. The data was variable with % CV ranging from 38% to 62%.

CDTL Comment:

Considering the variability in the exposure data, the exposure is comparable (but not the same or equivalent) among the three application sites. It should be noted that the Phase III study was conducted with all three application sites.

Transfer of Oxybutynin

The transfer study was conducted to assess the potential transfer of 84 mg oxybutynin from subjects treated with oxybutynin to their untreated partners through arm-to-arm contact by undressed or dressed arm in 14 couples (Study # SCO 5486).

The mean plasma concentration–time profiles of serum oxybutynin showed some exposure in the untreated subjects when they were in contact with treated subjects without clothing covering the application site with a mean (SD) C_{max} of 0.7 ± 0.5 ng/ml and AUC of 12.2 ± 8.6 ng.h/mL. However, no detectable concentrations of oxybutynin were observed upon contact among all dressed subjects, except for one who had one measurable concentration of 0.06 ng/mL (just above the LOQ of the assay of 0.05 ng/mL).

CDTL Comment:

There was no transfer of Oxybutynin gel (ANTUROL) seen in subjects with clothing. However there was minimal transfer to partners seen in subjects who applied the gel to areas without any clothing. Additionally, it is not possible to perform transfer studies in children under age of 18. Therefore, as there is a possibility of skin-to-skin transfer, Anturol Gel should not be used in children.

Effect of Sunscreen

The sunscreen study was conducted to assess the possible effect of sunscreen, applied 30 minutes before or 30 minutes after the treatment on the absorption of 84 mg oxybutynin applied to the abdomen (Study # SCO 5487). This was 3-period cross-over with a wash-out period of at least 14 days between treatments in 20 healthy subjects.

CDTL Comment:

There was no evidence of effect of sunscreen on the absorption of Oxybutynin Gel when it was applied 30 minutes before or 30 minutes after Oxybutynin Gel application.

Effect of Showering

Study SCO 5488 was conducted to assess the possible effect of showering at different times (1, 2, or 6 hrs) after daily application of 84 mg oxybutynin to the abdomen for 3 days. This study was designed as 4-period cross-over with no washing between treatment periods in 22 healthy subjects (11 couples).

The overall mean data showed no evidence of effect of showering on the absorption of oxybutynin at all treatment timepoints. The mean (SD) C_{max} was 14.28 ± 8.97, 15.14 ± 11.69, 16.90 ± 13.00, and 15.06 ± 9.43 and AUC was 220.285 ± 111.46, 188.66 ± 104.00, 207.88 ± 111.77, 201.74 ± 90.69 after no showering, 1, 2, and 6 hours after showering, respectively.

CDTL Comment:

It can be safely concluded that showering at 1, 2, or 6 hours after application of the gel had no effect on the absorption of oxybutynin.

Dose-systemic exposure relationships

The sponsor conducted Phase II study following a single and multiple doses to establish the PK and safety profiles of oxybutynin 3% gel at 42 mg, 60 mg, and 84 mg for 20 days in 48 healthy males and females subjects (Study # 1034-PhII, SCO 5241). The study was designed as three treatments, randomized, parallel group with 16 subjects in each group using the original formulation.

The gel was applied to the abdomen in all treatments. The last dose was on day 21. Blood samples were drawn on Day 2 and Day 21 immediately prior to dosing and at 2, 4, 8, 12, 16, 20, and 24 hours following dosing for analysis of serum oxybutynin and DEO levels. Additionally, on Day 22 to Day 26, blood samples were drawn at 36, 48, 72, 96 and 120 hours following dosing from Day 21. Pre-dose (trough) blood samples were also drawn on Days 2-20. Oxybutynin and DEO levels were analyzed by a validated LC-MS/MS method with LOQ of 0.05 ng/mL.

There was increase in plasma concentration of oxybutynin with increase in dose. However, there was no clear dose proportionality for Cmax and AUC.

CDTL Comment:

It appears increasing the oxybutynin dose was not necessarily associated with a proportional increase in exposure (i.e., not dose proportional). Thus, the absorption of oxybutynin may be limited by a skin permeability factor rather than the dose.

DSI Inspection:

No site inspections were requested by the Clinical-Pharmacology review team

6. Clinical/Statistical- Efficacy

Clinical Program for Efficacy

Study 20070060 was a 12-week double-blind, randomized, multicenter, placebo-controlled trial with a 24-week open-label extension phase, designed to evaluate the efficacy and safety of topically administered Anturol (Oxybutynin Gel) in patients with urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes.

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 of the two ^{(b) (4)} doses (56 mg and 84 mg) 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. Independent analyses of the submitted data sets of Study 20070060 were conducted by the primary medical officer to verify the sponsor's efficacy findings.

Indication

The sponsor seeks the indication of “*treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.*” *The sponsor is seeking this indication for*

(b) (4) 84 mg dose (b) (4)

6.1 Design and Efficacy Assessment

Design

Study 20070060 was a 12-week double-blind, randomized, multicenter, placebo-controlled trial with a 24-week open-label extension phase, designed to evaluate the efficacy and safety of topically administered Anturol gel (oxybutynin) in patients with urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes. Study participants who were at least 18 years old, with OAB symptoms for at least 3 months and who were either treatment naïve or had demonstrated a beneficial response to anticholinergic treatment for OAB, were eligible for study entry, provided all other inclusion/exclusion criteria were met. Patients were randomized in a 1:1:1 ratio to three treatment groups, Anturol (84 mg/day), Anturol (56 mg/day) and placebo. Patients were instructed to apply Anturol or placebo gel at approximately the same time each day during the study. Study drug was applied to the abdomen, inner and upper part of the thighs, or upper arms/shoulders.

Patient urinary diaries were filled out for treatment weeks 1, 2, 4, 8 and 12. Patients were reminded to start their urinary diary 5 days after receiving the first dose of study drug for the week 1 diary and 3 days prior to their next scheduled visit for all other diaries and to record urinary void volume on the first 2 days of the 3-day diary.

CDTL Comment:

The study design for the objective of efficacy assessment and the randomization as reviewed by the primary medical officer was acceptable.

6.2 Analysis of Endpoint(s)

Primary Endpoint

The primary efficacy endpoint was the change from baseline to Week 12 in the number of urinary incontinence events (UIE) UIE per week, as determined from a 3-day patient daily diary. UIE per week was computed from 3-day urinary diary.

CDTL Comment:

The primary end point was acceptable.

Secondary Endpoints

Secondary efficacy endpoints were:

- The change from baseline to Week 12 in the average daily urinary frequency based on the entries in the 3-day patients urinary diary;
- The change from baseline to Week 12 in the average urinary void volume per void based on entries from 2 consecutive days in the 3-day patient’s urinary diary.

CDTL Comment:

The secondary end points were acceptable.

Analysis of Primary Endpoint

Primary efficacy endpoint (UIE)

At Week 12, median change from baseline in weekly UIEs were -16.4 episodes experienced by patients in the Anturol 84 mg (b) (4) compared with -14.0 episodes in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in weekly UIEs (using Rank Transformation on values) was statistically significant (p-value = 0.0445, at the pre-specified 0.05 level 2-sided), in favor of Anturol 84 mg/day.



Table 3 - Analysis of change from baseline in UIE at Week 12 - ITT Population (LOCF)

Weekly UIE	n	mean(SD)	median	p-value ¹
Baseline				
Anturol 84mg/day	214	43.6 (27.90)	37.3	
(b) (4)				
Placebo	202	45.8 (31.87)	40.9	
Change from baseline				
Anturol 84mg/day	211	-20.4 (24.39)	-16.4	0.0445*
(b) (4)				
Placebo	192	-18.1 (28.81)	-14.0	

Source: Statistical reviewer’s analysis on ITT population

¹ p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with UIE (rank) baseline as covariate, treatment as factor.

* p-value is significant at 0.05 level, 2-sided

**p-value is not significant at pre-specified 0.025 level, 2-sided

Analysis of Secondary Endpoints(s)

There were two secondary efficacy endpoints proposed in the statistical analysis plan: 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.

Urinary Frequency

At Week 12, median change from baseline in average daily urinary frequency were -2.3 micturitions in the Anturol 84 mg group (b) (4), compared with -1.7 micturitions in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in average daily urinary frequency (using rank transformation on values) was statistically significant (p-value=0.0010) at pre-specified 0.0125 level 2-sided.

Table 4: Analysis of change from baseline in average daily urinary frequency (rank) at Week 12 - ITT Population (LOCF)

Average Daily Urinary Frequency	n	mean(SD)	median	p-value ¹
Baseline				
Anturol 84mg/day	214	11.3 (2.87)	10.7	
			(b) (4)	
Placebo	202	11.5 (3.34)	11.0	
Change from baseline				
Anturol 84mg/day	211	-2.6 (2.66)	-2.3	0.0010*
				(b) (4)
Placebo	192	-1.9 (3.34)	-1.7	

Source: Statistical reviewer's analysis on ITT population

¹ p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with urinary frequency (rank) baseline as covariate, treatment as factor.

* p-value is significant at 0.0125 level, 2-sided.

Volume of Urine per Void

At Week 12, median change from baseline in average urinary void volume were 26.6 mL in the Anturol 84 mg group (b) (4) compared with 5.7 mL in the placebo group; The LS mean difference between Anturol 84 mg and placebo in change from baseline in average urinary void volume (using rank transformation on values) was statistically significant (p-value<0.0001) at pre-specified 0.0125 level 2-sided.

Table 5: Analysis of change from baseline in urinary void volume (rank) at Week 12 - ITT Population (LOCF)

Average Urinary Void Volume (mL) per void	n	mean(SD)	median	p-value ¹
Baseline				
Anturol 84mg/day	209	196.9 (88.11)	189.2	
			(b) (4)	
Placebo	197	184.5 (85.71)	173.4	
Change from baseline - LOCF				
Anturol 84mg/day	206	32.7 (77.25)	26.6	<0.0001*
				(b) (4)
Placebo	187	9.8 (64.98)	5.7	

Source: Statistical reviewer's analysis on ITT population

¹ p-value is for the estimated LS mean difference vs. placebo from a rank-ANCOVA model with urinary void volume (rank) baseline as covariate, treatment as factor.

* p-value is significant at 0.0125 level, 2-sided.

CDTL Comment:

In summary:

- *Comparing to placebo, Anturol 84 mg/day showed statistical significant reductions in the number of UIE per week (16.4) and the daily urinary frequency (-2.3), and statistical significant increase in the average urinary void volume(26.6) at Week 12;*
- *Comparing to placebo, Anturol 56 mg/day failed to show statistically significant results on the primary and secondary efficacy endpoints at Week 12.*

Therefore, results of study 20070060 provided statistical evidence of efficacy for the Anturol gel 84 mg/day in the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. However, Anturol gel 56 mg/day failed to demonstrate statistically significant efficacy, after adjusting for multiplicity, in the same patients studied.

6.3 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 6: 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)

Source: MO Review

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

CDTL Comment:

Subject discontinuation rate is within the acceptable range.

6.4 Statistical Review

Drs. Jia Guo and Mahboob Sobhan from the Division of Biometrics III, reviewed the efficacy data from study 2007060 and found the efficacy data supported use of the Anturol 84mg dose only.

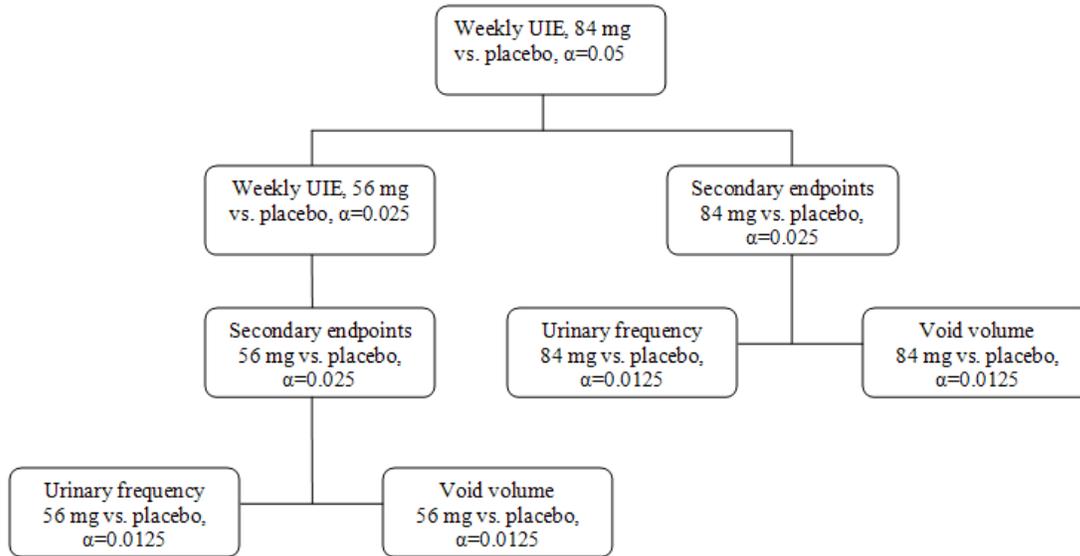
Statistical Issues:

A Final Statistical Analysis Plan (SAP) was signed off on June 17th, 2011. In this SAP, a closed testing principle was adopted by the Applicant for testing the primary and secondary endpoints to control the overall type I error. First, the testing would be conducted between Anturol 84mg/day vs. placebo on the change from baseline in the number of UIE per week. If this test is statistically significant at the 0.05 level (2-sided), then the following tests would be conducted respectively. The primary and secondary efficacy analyses were based on the ITT population.

Due to the non-normality of the data for the change from baseline in the number of UIE at each visit, the reviewer's analyses were also based on the rank-transformed UIE data. But in the reviewer's analysis, the rank transformed change from baseline in the number of UIE at Week 12 was analyzed by an analysis of covariance (ANCOVA) model with ranked baseline number of UIE as a covariate and treatment group as a factor. The comparison between Anturol 84 mg/day vs. placebo and 56 mg/day vs. placebo was based on the estimated LS mean difference of the (transformed) mean change from baseline in UIE per week at Week 12. Last observation carried-forward (LOCF) method was used to impute the missing values of number of UIE at Week 12 before transformation was done.

The secondary endpoints were analyzed in the same way using the ANCOVA model described above with the corresponding ranked baseline of the endpoint as a covariate and treatment group as a factor in the model (See Figure 1 below).

Figure 1: Testing Sequence for Primary and Secondary Efficacy Endpoints



Source: Modified from Applicant's statistical analysis plan (06/10/2010, α is the pre-specified level for a 2-sided test.

The Biometrics review team summarized the efficacy analysis issues for this application as follows:

- The applicant provided two statistical analysis plans to adjust for multiplicity in this application: one pre-specified prior to data base lock (modified ITT) and a modified version after the data base was unblinded. The modified version after the data was unblinded included the following changes:
 1. The applicant applied the Mixed Model Repeated Measures (MMRM) analysis based on the rank-transformed data of the efficacy endpoints due to the non-normality of data. This analysis approach, i.e., MMRM based on rank data was neither well understood (established) in the literature nor in the application. No literature or supported information was submitted by the applicant. The applicant should have fully investigated performance of the MMRM under null or alternative hypotheses before its use.
 2. Applicant's analysis was based on the modified ITT population rather than the ITT population for the primary efficacy analyses. The modified ITT population defined by the applicant may not represent the potential target population of this test drug.

Regarding the first issue, the applicant provided the data base lock and data unblinding dates in response to the Agency's information request on Oct. 27, 2011. According to the information from the applicant, the study data was unblinded on June 21, 2010. Therefore, the amendment that proposed the sequence of closed testing of the primary and secondary endpoints for the two doses was a post-hoc analysis. Hence, this MMRM analysis was not acceptable for consideration in the statistical review by the Agency.

Regarding the second issue, the statistical reviewer did not agree with the applicant’s post-hoc analysis plan of using an m-ITT population, because changes in the hierarchy of testing hypotheses using closed testing procedures after the blind is broken is not acceptable.

Therefore, the statistical reviewer conducted the efficacy analyses for both the 56 mg and 84 mg doses using rank-ANCOVA model using the entire ITT population.

The statistical reviewer’s results are outlined in Table 7 below. The primary efficacy endpoint i.e. change from baseline to Week 12 in the number of UIE per week, and two secondary endpoints, change from baseline to Week 12 in the average daily urinary frequency and change from baseline to Week 12 in the average urinary void volume per void for study 20070060 using the final statistical analysis plan are as follow:

- Compared to placebo, Anturol 84 mg/day showed statistical significant reductions in the number of UIE per week and the average daily urinary frequency, and statistical significant increase in the average urinary void volume per void at Week 12;
- Compared to placebo, Anturol 56 mg/day failed to show statistically significant results on the primary and secondary efficacy endpoints at Week 12.

Table 3: Mean (SD) and median change from baseline to Week 12 in incontinence episodes, urinary frequency, and urinary void volume: Intent-To-Treat population (LOCF*)

Parameter	Placebo (N=202)		Anturol Gel (84 mg/day) (N=214)	
	Mean (SD)	Median	Mean (SD)	Median
Weekly Urinary Incontinence Episodes				
Baseline	45.8 (31.87)	40.9	43.6 (27.90)	37.3
Reduction	-18.1 (28.81)	-14.0	-20.4 (24.39)	-16.4
Mean difference [Anturol – placebo] (SE)			-2.3 (2.65)	
P-value [†] vs. placebo			0.0445 ^a	
Daily Urinary Frequency				
Baseline	11.5 (3.34)	11.0	11.3 (2.87)	10.7
Reduction	-1.9 (3.34)	-1.7	-2.6 (2.66)	-2.3
Mean difference [Anturol – placebo] (SE)			-0.7 (0.30)	
P-value [†] vs. placebo			0.0010 ^b	

(b) (4)

Urinary Void Volume (mL)				
Baseline	184.5 (85.71)	173.4	196.9 (88.11)	189.2
Increase	9.8 (64.98)	5.7	32.7 (77.25)	26.6
Mean difference [Anturol – placebo] (SE)			23.0 (7.24)	
P-value [†] vs. placebo			<0.0001 ^b	

(b) (4)

*Last-Observation-Carried-Forward imputation for missing data

[†] P-value is based on ANCOVA analysis on rank-transformed data

^a Comparison is significant if $p \leq 0.05$

^b Comparison is significant if $p \leq 0.0125$, adjusting for multiplicity

^c Comparison is significant if $p \leq 0.025$, adjusting for multiplicity

Statistical Reviewer's Comments:

Based on the change from baseline in number of UIE, average daily urinary frequency and average urinary volume per void Week 12, the results of study 20070060 provided statistical evidence of efficacy for the Anturol 84 mg/day, and failed to demonstrate the efficacy of Anturol 56 mg/day, in terms of treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. At Week 12, median change from baseline were -16.4 episodes in weekly UIEs, -2.3 micturitions in average daily urinary frequency, and 26.6 mL in average urinary void volume in the Anturol 84 mg group, compared with -14.0 episodes in weekly UIEs, -1.7 micturitions in average daily urinary frequency, and 5.7 mL in average urinary void volume in the placebo group.

CDTL Comment:

Patients treated with ANTUROL 84 mg experienced a statistically significant decrease in the number of urinary incontinence episodes (UIE) per week from baseline to endpoint (the primary efficacy endpoint) compared with placebo ($p=0.0445$). Statistically significant improvements in daily urinary frequency ($p=0.0010$) and urinary void volume ($p<0.0001$) were also seen with 84mg ANTUROL relative to placebo support the efficacy of the 84 mg dose. The mean difference from placebo for the 84 mg dose was -2.3 for urinary incontinence episodes per week in a group of patients with greater than a mean of 40 incontinence episodes per week at baseline.

Patients treated with ANTUROL 56 mg did not experience a statistically significant decrease in the number of UIE per week from baseline to endpoint (the primary efficacy endpoint) compared with placebo ($p=$). This dose failed to achieve a statistically significant improvement in either daily urinary frequency or urinary void volume compared to placebo.

Handling of Missing Data:

Missing values for diary data were estimated using the mean of remaining non-missing values for the 3-day interval as long as there was only 1 of 3 values missing. In case of 2 or 3 days of diary missing, the diary evaluation for that clinical visit was set to missing.

Missing void volumes and missing urinary urgency were not imputed for any urinary episodes. Any analysis performed for the urinary urgency or urinary void was based on observed values only and excluded those urinary episodes that had missing values for the corresponding endpoint.

If a patient had less than 2 days of void volume and urinary urgency data prior to randomization (i.e., baseline data), those patient will be excluded from the analysis of these parameters.

CDTL comment:

The handling of missing data was acceptable to the Statistical review team.

7. Safety

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 which included use of the to-be-marketed formulation.
2. The 120-day Safety Update

CDTL Comment:

The data were pooled from the formulation (b) (4) and to be marketed formulation (b) (4) (b) (4) as agreed upon by the agency. However, the primary assessment of safety as reflected in the PI is derived from use of the to-be-marketed (TBM) formulation.

7.1 Safety Population and Overall Exposure

Patient exposure

For the purposes of exposure to the oxybutynin gel, results from patients using the original and to-be-marketed formulations were pooled. 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 12- week 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, accounting for almost 70% of the total exposure in drug development and the only part of this exposure was with placebo controlled subjects.

Table 8: 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

Source: Sponsor’s NDA submission

The demographics and baseline characteristics for Study 20070060 and its open label extension (OLE) are shown in Table 9. 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.

7.2 Demographics

Table 9: Patient demographics and baseline characteristics for Study 20070060 and the open label extension (OLE).

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

Source: ISS from Sponsor's Submission

CDTL Comment:

The pooled patient population in study 20070060 represents adequate exposure to oxybutynin gel.

7.3 Adverse Events

Serious Adverse Events

There were no serious adverse events (SAEs) 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 these SAEs were thought to be related to the study drug.

CDTL Comment:

The Primary Medical officer reviewed all of the case narratives for these subjects and agreed with the investigators conclusion that none of them were related to the study drug. I concur with the Primary MO.

Deaths

There were no deaths reported.

Adverse Reactions Leading to Discontinuation

There were no dropouts due to adverse reactions in the Phase 1 and 2 studies with either the original or TBM formulation. 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 reactions, which accounted for one third of the dropouts due to adverse events, followed by gastrointestinal and nervous system disorders. All of these adverse reactions were mild and reported to be resolved.

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 10 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 10: Common adverse reactions in the randomized, double-blind, placebo-controlled 12-week study

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
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

Source: Medical officer analysis

CDTL Comment:

The adverse reactions seen with Anturol were very similar to those seen with other anticholinergics. However, application site erythema and rash are typical for a topical gel.

Application site reactions

The sponsor evaluated application site reactions through investigator reporting. The sponsor separated 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. 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 11: Application site adverse reactions reported for subjects in Study 20070060 reported as events

	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)

Source: MO Review

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).

CDTL Comment:

The erythema reported with the to-be-marketed formulation was mild to moderate. No subject was reported to have developed severe erythema, rash or any other type of severe skin reaction with the to-be-marketed formulation. Overall, the to-be-marketed drug product is safe for use in patients with overactive bladder syndrome.

8. Advisory Committee Meeting

No Advisory Committee meeting was held for this new application.

9. Pediatrics

The sponsor requested a full waiver for a pediatric assessment for all pediatric age groups. The Division forwarded the request to PeRC PREA subcommittee.

The PeRC agreed with the Division to grant a full waiver for Anturol because it does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients.

CDTL Comment:

It should be noted that there are approved oral oxybutynin products available for children, but there are insufficient data for treatment in pediatric population under age 5 years. Therefore, oral oxybutynin is not recommended for age group under 5 years of age and ANTUROL gel should not be used in children.

10. Postmarketing Experience

The product is not approved in any other country, therefore, no postmarketing data is available.

11. Other Relevant Regulatory Issues

Division of Scientific Investigation (DSI)

No request for inspection of the clinical and/or analytical sites was made to the Office of Scientific Investigations.

Office of Drug Promotion (OPDP)

OPDP reviewer, Janice Maniwang, reviewed both the PI and the PPI and provided valuable input with recommendations. All pertinent recommendations from OPDP were discussed by the clinical team and incorporated into the draft label/PPI.

Division of Risk Management (DRISK)

Shawna Hutchins, the DRISK reviewer, reviewed both draft PI and PPI and recommended changes to the PPI. The suggested changes were incorporated into the PPI.

Division of Medication Error Prevention and Analysis (DMEPA)

DMEPA concludes the proposed proprietary name (ANTUROL) is acceptable from both a promotional and safety perspective.

DMEPA LABELING RECOMMENDATIONS

Recommendations for revisions for the package insert communicated during the labeling meetings included removal of all trailing zeros, and revision of the presentation of the dosage form and strength information in the Prescribing Highlights and Full Prescribing Information. DMEPA also recommended revising the presentation of the product information in the How Supplied section of the package insert to include the different container sizes.

CDTL Comment:

DMEPA recommendations were incorporated into the package insert.

DMEPA also made recommendations for the Carton labeling, which were also incorporated by the Division and agreed by the sponsor (See proposed Carton label below).



12. Labeling

Key labeling changes:

Highlights of PI:

Dosage and Administration

Apply three pumps of Anturol (84 mg) once daily to clean and dry, intact skin on the abdomen, or upper arms/shoulders, or thighs.

Warnings and Precautions

Urinary Retention

Gastrointestinal disorders

Flammable Gel

Myasthenia Gravis

Angioedema

Adverse Reactions

Most common adverse reactions >3% are

Application site reactions

Dry mouth

Use in Specific Populations

Anturol should not be used in children because safety and effectiveness have not been established in pediatric patients.

FPI

Clinical

Patients treated with Anturol (84 mg) experienced a statistically significant decrease in the number of urinary incontinence episodes per week from baseline to endpoint when compared to placebo, p-value 0.0445 and patients treated with the 56mg dose did not show statistically significant efficacy. Statistically significant improvements in daily urinary frequency (p=0.0010) and urinary void volume (p<0.0001) were also seen with 84mg ANTUROL relative to placebo.

CTDL Comment:

Copy of the draft label was sent to the sponsor on November 7th, 2011 and received back on November 16th with their edits. The SEALD review team concurred with labeling November 30, 2011. The label was finalized on November 30th, 2011.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

In my opinion, the sponsor has provided sufficient evidence for efficacy and safety in support of NDA # 202-513. Therefore:

- 1. An approval action should be granted for Anturol 84mg dose.*

(b) (4)

Risk Benefit Assessment

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

Oxybutynin 3% gel (56 mg) did NOT demonstrate statistically significant efficacy for its primary endpoint and key secondary efficacy endpoints. No significant safety issues were detected with the 56 mg dose.

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 gel 3% in patients with overactive bladder (OAB). The primary objective was to compare the effects of oxybutynin gel relative to placebo in patients with urge incontinence episodes. The primary efficacy endpoint was the change from baseline at the end of study in the number of urinary incontinence episodes (UIE) 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.

In Study 20070060, the mean placebo effect was -18.1 episodes per week, compared to -20.4 in the 84 mg oxybutynin treated group ($p=0.0445$). The magnitude of the difference between active drug and placebo was small, reduction of 2.3 episodes per week. This result (2.3) although small, is clinically an acceptable evidence of a statistically meaningful outcome.

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 this 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 topically applied 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:

- 1) The data submitted by the Sponsor is adequate to allow the reasonable conclusion that Oxybutynin gel 3% (at the 84 mg) is a safe and effective treatment for patients with the symptoms of overactive bladder.

(b) (4)

CDTL Comment:

The primary Medical Officer's assessment of risk and benefit concurred with my assessment above.

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

/s/

SURESH KAUL
12/06/2011

AUDREY L GASSMAN
12/06/2011