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APPLICATION NUMBER:

202513Orig1s000

SUMMARY REVIEW

Acting Deputy Division Director Summary Review

Date	December 7, 2011
From	Audrey Gassman, MD
NDA #	202-513
Applicant name	Antares Pharma, Inc.
Submission dates	December 20, 2010 (submitted) February 8, 2011 (received)
PDUFA goal date	December 8, 2011
Proprietary name/established name	Anturol/oxybutynin chloride
Dosage Form/strength	Transdermal gel/3% (84 mg) applied as three pumps once daily
Proposed Indication	Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency
Action	Approval of the 84 mg dose (b) (4)

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Suresh Kaul, MD, MPH
Medical Officer Review	Jonathan P. Jarow, MD
Statistical Review	Jia Guo, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Laurie McLeod-Flynn, PhD Lynnda Reid, PhD
Clinical Pharmacology Review	Sayed Al Habet, RPh, PhD Myong-Jin Kim, PharmD
CMC Review	Bogdan Kurtyka, PhD Moo-Jhong Rhee, PhD
OSE/DMEPA	Walter Fava, RPh, MSEd Carlos Mena-Grillasca, RPh Carol Holquist, RPh
ONDQA Biopharmaceutics	Tapash Ghosh, PhD Angelica Dorantes, PhD
DMPP	Shawna Hutchins, MPH, BSN, RN LaShawn Griffiths, RN, MSHS-PH, BSN Melissa Hulett, RN, BSN, MSBA
OPDP	Janice Maniwang, PharmD, MBA Jina Kwak, PharmD
Office of Scientific Investigations	Not requested
SEALD	Jeannie Delasko, RN, MS Laurie Burke, RPh, MPH

OND=Office of New Drugs
OPDP= Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DMPP=Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader
DEPI=Division of Epidemiology
PMHS=Pediatric and Maternal Health Staff
DRUP=Division of Reproductive and Urologic Products
OSI=Office of Scientific Investigations

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1. Introduction

Overactive bladder (OAB) is a symptom complex which consists of urinary frequency and urgency incontinence. Anticholinergic drugs (muscarinic antagonists) have been a mainstay of OAB therapy for decades. The mechanism of action of these anticholinergic drugs is blockade of cholinergic (muscarinic) receptors in the bladder detrusor muscle and, therefore, inhibition of bladder contractility. The subject of this NDA (#202513) review, Anturol (oxybutynin chloride), is an anticholinergic drug product that is proposed for the treatment of OAB.

Oxybutynin chloride (Ditropan) tablets were initially approved for the symptomatic treatment of OAB in 1975. Since the initial approval of Ditropan in 1975, other formulations of oxybutynin have subsequently been approved, including an extended release formulation (Ditropan XL). More recently, transdermal formulations of oxybutynin (such as Oxytrol and Gelnique) were developed in an attempt to reduce some of the systemic anticholinergic side effects and improve patient compliance. There are currently two approved transdermally applied oxybutynin products: Oxytrol, which is a transdermal delivery system and, Gelnique, which is a topically-applied gel formulation.

In addition to oxybutynin products, other currently approved products for treatment of OAB include tolterodine (Detrol), solifenacin (VESIcare), darifenacin (Enablex), trospium (Sanctura), fesoterodine (Toviaz) and onabotulinumtoxin A (Botox). Of the available products for OAB, oxybutynin is the only product available for the treatment of OAB that is available in different transdermal formulations.

2. Background

The Division held several key meetings with the sponsor during drug development of the oxybutynin gel which are summarized below:

On February 9, 2005, a pre-IND meeting was held. At that meeting, the sponsor provided an introductory overview of their product development plan and identified questions for the Agency. The sponsor received guidance from the Clinical, Statistics, Clinical Pharmacology and CMC review teams on their proposed product development. At that meeting, the Division recommended a Phase 2 study to further justify dose finding prior to initiation of a phase 3 study. On April 7, 2005, a follow-up meeting was held between the sponsor and the Clinical and Clinical Pharmacology divisions to further clarify specific recommendations from these disciplines regarding a proposed phase 2 study protocol.

On March 11, 2005, the sponsor officially opened IND 70,527 with a phase 2 dose-ranging study protocol in healthy volunteers. On April 6, 2005, comments from the Division on the phase 2 protocol related to sample size, trial duration and testing a third dose (60 mg) were discussed with the sponsor. The sponsor faxed a revised phase 2 protocol to the Division on April 8, 2005. The Division concurred with the revised protocol with no additional comments.

On May 2, 2006, an EOP2 meeting was held with the sponsor. At that meeting, the Division stated that, following further internal discussion, the acceptable regulatory pathway for development of the oxybutynin gel was the 505(b)(1) application. The Division recommended that two phase 3 studies be performed, although as an alternative, the sponsor was given the option of performing only one phase 3 trial. The Division stated that the results would need to be both clinically and statistically significant results. The Division also noted that the definition of what would be considered "clinically significant" would be a review issue.

Comment: The issue of whether the application would be submitted as a 505(b)(1) or 505(b)(2) was further discussed during drug development. Specifically, the acceptability of using a 505(b)(2) approach was discussed in responses to a September, 2009, EOP2 meeting package (See preliminary comments from the Division dated October 22, 2009). Guidance to the sponsor on a possible 505(b)(2) approach was outlined to the sponsor in those EOP2 comments.

On August 11, 2006, the sponsor submitted a special protocol assessment (SPA) for a Phase 3 protocol (Protocol 20040077). Protocol 20040077 was entitled, "A Double-Blind, Randomized, Parallel, Placebo-Controlled, Multicenter Study Evaluating the Effect of 12 Weeks of Treatment with Topically Administered Oxybutynin Gel in Patients with Urge and Mixed Urinary Incontinence". Final agreement was not reached on the phase 3 SPA, but recommendations and advice from the Clinical Pharmacology, Clinical, and Statistical review teams were sent to the sponsor in a regulatory letter on September 22, 2006.

Comment: The September, 2006, letter did state that agreement was reached between the sponsor and the division on the primary endpoint and study duration of the phase 3 trial.

Several revisions to the phase 3 protocol, including the addition of a second, lower dose, were requested by the Division and a revised phase 3 protocol (#20070060) based on the Division's comments 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.

In May, 2008, the sponsor submitted a revised statistical analysis plan that proposed a new interim analysis for their ongoing phase 3 trial (Study #20070060). The Clinical and the Statistical review teams reviewed the submission. On August 21, 2008, an Advice letter was sent to the sponsor stating that the proposed interim analysis plan was not acceptable.

On September 25, 2008, the sponsor submitted a notification to DRUP that trace levels of the potentially carcinogenic impurity, [redacted] (b) (4) had been identified in the formulation of oxybutynin gel, 3.0% being used in the Phase 3 overactive bladder (OAB) trial (Study # 2007060). The original oxybutynin gel, 3.0% formulation contained [redacted] (b) (4) The submission also contained a request for guidance regarding the use of a modified [redacted] (b) (4) oxybutynin gel, 3.0% formulation to treat the remaining patients to be enrolled in Study 2007060. At the time of the submission, 130 subjects had been dosed with the original [redacted] (b) (4) formulation.

At a meeting on December 4, 2008, to discuss the [redacted] (b) (4) impurity, the Division stated that, "pooling of data from the 130 patients treated with the old formulation with the remaining 470 patients to be enrolled (and treated with the new formulation) will be acceptable if the old and new oxybutynin gel, 3% formulations are shown to be bioequivalent in an in vivo study."

Comment: On September 23, 2009, the sponsor submitted results of a bioequivalence study (SCO 5432) to bridge the pharmacokinetics of the old and new gel formulations. The two formulations were not bioequivalent. The Clinical Pharmacology reviewer evaluated the pharmacokinetic profiles from the two formulations in this study and stated that, "Based on systemic exposure, it appears that it appears that it would be reasonable to allow pooling. The excesses in AUC beyond BE criteria are only marginal. The safety of the higher Cmax from the revised formulation will be captured in the remaining phase 3 patients dosed with the new formulation." Therefore, the Clinical Pharmacology review team concluded that the bridging data from the pK study was sufficient to allow data from the two phase 3 formulations in the Phase 3 study to be pooled (See Clinical Pharmacology review to IND 70,527 dated November 9, 2009).

On October 22, 2009, follow-up preliminary comments were sent to the sponsor about the ongoing development program. Specifically, in response to a question on pooling data from the 130 patients treated with the previous (old) formulation with the rest of the data (about 480 patients) with the modified formulation, the following response was noted, "We agree that the phase 3 data from the two formulations can be pooled. Please include a flag designating if the subject received the old or new formulation of the drug product

in all datasets that are submitted with the NDA." Additional comments that were conveyed to the sponsor also included advice to conduct phase 1 studies to address possible transfer of gel to others, use of other topical agents as sunscreen, and washing procedures.

The NDA submission was considered officially received on February 8, 2011, after receiving a small business waiver, and was subsequently filed on April 6, 2011. In the submission, the Applicant stated that the oxybutynin gel will be supplied in a metered dose pump delivering 28 mg of oxybutynin per actuation. The Applicant proposed (b) (4) (b) (4) an 84 mg (3 actuations) daily alternating among three sites: abdomen (reference site), (b) (4) thighs and upper arms and shoulders.

Comment: The Sponsor conducted a phase 1 study to assess the effect of application site on the absorption of oxybutynin (#OXBTN/2006/223). Based on the exposure data, the relative bioavailability among the three application sites of oxybutynin and its metabolite, N-desethyl oxybutynin was determined to be comparable. The phase 3 trial, 20070060, was conducted using all three application sites.

3. CMC

The CMC review team concluded in their review dated October 7, 2011, that, "This NDA has **not** 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 not have adequate information as required. Therefore, from a CMC perspective, this NDA is not recommended for approval in its present form until the issues listed in the "List of Deficiencies" are resolved."

The three issues that were listed as deficiencies in the October, 2011, CMC review that comprised the basis for the Non-Approval recommendation included:

- The specification of the drug product is not adequate due to unresolved issues on the diffusion rate acceptance criterion (pending Biopharm's recommendation).
- Container/closure system is different from that used in the clinical batches, and it has not been demonstrated whether the new (b) (4) will have any adverse effect on the drug product.
- Labels/labeling do not have required information.

A teleconference with the sponsor was held on November 2, 2011, to resolve the outstanding drug product specification issues. The sponsor responded via Email on November 7, 2011, and accepted the Agency's recommended acceptance criteria for the in vitro drug release rate test. A formal amendment with the new acceptance criteria was submitted on November 9, 2011.

In an addendum to their review dated November 15, 2011, the Biopharmaceutics reviewer stated that, "ONDQA-Biopharmaceutics evaluated the information provided as

of November 9, 2011, to support the approval of NDA 202-513 for Anturol (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."

In an Addendum to their October 12, 2011, review, the CMC reviewers stated that, "The sponsor addressed above issues satisfactorily in the submissions dated 07-Oct-2011, 09-Nov-2011 and 01-Dec-2011. Therefore from the ONDQA perspective, this NDA is now recommended for Approval."

Comment: I concur with the recommendations of the CMC review team. There are no outstanding CMC, Compliance or Biopharmaceutics issues.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team stated in their review dated September 22, 2001, that, "There is no impediment to approval of this application from a Pharmacology/Toxicology perspective."

Comment: I concur with the recommendation of the pharmacology/toxicology review team. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology

The sponsor initially conducted several clinical pharmacology studies with the original oxybutynin gel 3% formulation. Key clinical pharmacology studies included:

- A phase 1 study of the following doses: 2 grams (60 mg) versus 1 gram (30 mg) gel per day for 7 consecutive days (Study #OXPK2)
- A phase 1 study to assess the pharmacokinetics of oxybutynin gel (84 mg/day) when applied to different skin sites (#OXBTN/2006/223)
- A phase 2 study (dose escalation) at the following doses: 42 mg, 60 mg, and 84 mg (every morning) (Study #1034-PhII)

1. Study #OXPK2 was a pilot study in 8 healthy female subjects to determine the bioavailability of oxybutynin from two different doses of oxybutynin 3% gel designated TEST1 [oxybutynin 60 mg; 2 g; 3%] and TEST2 [oxybutynin 30 mg; 1 g, 3%]) over 7 days of treatment. The study employed a dose escalating design with the two treatment periods separated by a wash-out period of one week between dosing periods. In all treatments, the drug was administered once daily over the 7 day treatment period. The mean AUC increased from approximately 75 to 164 ng/mL.h and Cmax from 4.71 to 9.34 ng/mL with increase in dose from 30 mg to 60 mg oxybutynin, respectively (i.e., approximately 2 fold increase).
2. Study #OXBTN/2006/223 was a single dose, open label, comparative, three-way application site cross over pharmacokinetic study in 30 healthy subjects that used one dose of oxybutynin gel (84 mg/day). This study compared the pharmacokinetics of oxybutynin when the gel was applied to three different application sites: inner and upper thighs, upper arms and shoulders and the

abdominal area. The sponsor reported that the results of this study suggested that the relative bioavailability of the three application sites, in terms of oxybutynin and n-desethyloxybutynin (DEO), were comparable.

3. Study #1034-phII was a dose escalating study in 48 healthy males and females conducted to evaluate single-dose and multiple-dose PK and safety profiles at three doses: 42 mg, 60 mg and 84 mg/day for 20 days. The report concluded that there was an increase in exposure with doses (42, 60, and 84 mg) for both oxybutynin and its active metabolite. In addition, the mean Cmax concentration of oxybutynin at Day 20 was approximately 4.5, 6.3, and 7.3 ng/mL and AUC was 72.5, 102.8, and 130.0 ng.h/mL following 42, 60, and 84 mg doses, respectively. This study reported that the Cmax did not increase substantially after the 20th dose for any of the doses studied.

Clinical Pharmacology reviewed the data from these clinical pharmacology studies using the original formulation (See Clinical Pharmacology review dated October 13, 2011). With respect to Study #OXBTN/2006/223, the Clinical Pharmacology review stated the following, "The exposure was highest after application of the gel to arms and shoulders compared to abdomen and thighs. The mean (SD) Cmax 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 were variable with %CV ranging from 38% to 62%. Considering the variability in the data, the exposure would be comparable (but not the same or equivalent) among the three application sites. It should be noted that Phase III study was conducted with the three sites."

Comment: The Clinical Pharmacology reviewers concurred with the sponsor that absorption from the three application sites was comparable (See Clinical Pharmacology review dated October 13, 2011). Use of all three application sites is included in the Dosing and Administration section of the agreed to Anturol label.

The sponsor changed the oxybutynin formulation for Anturol [redacted] (b) (4) The sponsor was subsequently asked by the Clinical Pharmacology review team to perform three new phase 1 studies with the to-be-marketed formulation (showering, transfer and sunscreen application), and a phase 2 bioequivalence study between the formulations. A total of 4 phase 1 and 2 studies related to the to-be-marketed formulation were submitted and reviewed by the Clinical Pharmacology review team.

These four phase 1 and 2 studies that evaluated to to-be-marketed formulation are outlined briefly below:

1. <u>Showering study (SCO 5488)</u>

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 [redacted] (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. 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.

Comment: The Clinical and Clinical Pharmacology review teams concluded that there was an effect of showering after application upon the bioavailability of the drug product, but that this will be addressed in labeling.

2. Sunscreen study (SCO 5487)

An open-label, three-period, single dose, crossover study was performed in 20 healthy subjects in Germany to determine the effect of sunscreen application on the bioavailability of a single dose of transdermal oxybutynin gel. The study compared pharmacokinetics after application of a single dose of oxybutynin gel (84 mg) to application of a single dose of oxybutynin gel 30 minutes before application of sunscreen to the same skin are to a single dose of oxybutynin gel 30 minutes after application of sunscreen to the same skin area.

Comment: The Clinical Pharmacology determined that there was no difference in the exposure (Cmax and AUC) between the three treatments with and without sunscreen (See Clinical Pharmacology review dated October 13, 2011). The lack of effect of sunscreen application on systemic exposure will be addressed in product labeling.

3. 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) with one partner receiving a single dose (84 mg) of oxybutynin gel. The gel was applied to one arm of a subject, and the partners then had vigorous arm-to-arm contact for 15 minutes. Pharmacokinetic sampling was done when the subject who received the gel had a treated arm that was bare, and again when the treated arm receiving the gel was clothed. The untreated partners had bare arms during both treatments.

There were detectable levels of serum oxybutynin in the untreated partners who had arm-to-arm contact with their treated partner. However, no detectable serum levels were observed in untreated subjects when their partners had clothing on their arms.

Comment: The Clinical and Clinical Pharmacology review teams concluded that the effect of potential transfer to other non-treated persons can be addressed in product labeling. I concur with their assessment.

4. Bridging pharmacokinetic study for the new formulation [redacted] (SCO 5432)

After completing dosing in 130 patients in the phase 3 trial, the sponsor identified presence of trace amounts of the potential carcinogenic impurity [redacted] Division, in conjunction with the Clinical Pharmacology reviewers, determined that the sponsor could continue dosing subjects in phase 3 trial (Study 20070060) with the new formulation [redacted] but that bridging data should be submitted to justify pooling of data from the 130 patients who received the [redacted] formulation with the remaining phase 3 patients (N = 480) who will receive the new formulation of Anturol.

The bridging study between the original and to-be-marketed formulations was designed as an open-label, 2-period, crossover study and was performed to determine bioequivalence between the two formulations [redacted] 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] had an AUC that was 16% higher than the original and a Cmax that was 24% higher. The 90% confidence interval was outside the pre-specified criteria for bioequivalence.

At the time of completion of the bridging study, the Clinical Pharmacology reviewers evaluated the results from the sponsor and made the following conclusions, "Systemic bioavailability was higher from the revised formulation. Cmax and AUC were higher on average by 23 % and 15 % respectively. For AUCτ, the point estimate and the 90 % C.I. for the estimate were generally contained within the acceptance range for BE (80- 125 %), although the upper bound of C.I. marginally exceeded the accepted limit (126.5 % vs. 125 %). Formulations were not BE with respect to Cmax. The primary purpose of this BE study was to pool data from the completed 130 phase 3 patients with data obtained using the revised formulation. Based on systemic exposure comparisons, it appears that it would be reasonable to allow pooling. The excesses in AUC beyond BE criteria are only marginal. The safety of the higher Cmax from the revised formulation will be captured in the remaining phase 3 patients dosed with the new formulation." (See Clinical Pharmacology review finalized in IND 70,527 dated November 9, 2009)

After review of the three phase 1 and one phase 2 (bridging) studies above, the Clinical Pharmacology reviewers concluded in their review dated October 13, 2011, that, "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."

Comment: In an Email dated December 2, 2011, the Clinical Pharmacology review team stated that they had "no additional comments" on the final label. I concur with the recommendations of the Clinical Pharmacology review team. There are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

No clinical microbiology consult was requested.

7. Efficacy/Statistics

In support of efficacy of Anturol (oxybutynin chloride) gel, the sponsor submitted the results of one large (626 subject), randomized, placebo-controlled trial (hereafter referred to as Study 20070060) and supportive pharmacokinetic data. Study 20070060 was a multicenter (63 United States sites), prospective, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of two doses of oxybutynin gel 3% for the symptomatic improvement of OAB after 12 weeks of treatment.

Brief Overview of the Study Design:

Study 20070060 evaluated two doses of oxybutynin gel (56 mg and 84 mg) and compared each dose to placebo gel. Eligible patients were randomized in a blinded fashion in blocks of 6. Each block of six randomized 2 subjects to 56 mg/day of oxybutynin gel, 2 subjects to 84 mg/day of oxybutynin gel and 2 subjects to placebo gel (1:1:1). Patients self-administered 3 mL of gel containing either oxybutyin or placebo daily from 3 pump bottles to rotating sites on the abdomen, arm/shoulder area or thigh area for 12 weeks during the 12 week double-blind period. In addition, a 24-week open-label safety extension period to evaluate safety and skin irritation profile from 78 subjects from subjects who successfully completed 12 weeks of administration of either oxybutynin (56 mg or 84 mg/day) or matching placebo gel was also completed.

Comment: The study design for the objective of efficacy assessment and the randomization was reviewed by the Clinical reviewer and CDTL and was determined to be acceptable for this OAB indication.

Inclusion/exclusion criteria for Study 20070060:

The study population for Study 20070060 consisted of 626 subjects who were at least 18 years of age with a history of overactive bladder symptoms for at least three months. Symptoms of OAB were evaluated during screening by history and during treatment by a 3-day urinary patient diary.

Key Inclusion Criteria included:

- 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

Key Exclusion Criteria included:

- 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 UTI at screening or more than 3 treated UTIs within the past 12 months
- Lower urinary tract surgery within last six months
- Diagnosis of interstitial cystitis (IC) or painful bladder syndrome

Patient Demographics and Baseline Characteristics for Study 20070060:
The demographics and baseline characteristics for subjects are listed in Table 1.

Table 1: Demographics of subjects enrolled into Study 20070600*

	Study 20070600
N (Total)	626
Age – Median	59
Age range (years)	19 to 89
BMI	32 ± 7
Race (%)	White - 87 AA - 11 Asian - 1 Other – 1
Gender –Male n(%) Female n(%)	84 (13) 542 (87)

*Adapted from the Clinical review, Table 14.

Subject disposition for Study 20070060:

A total of 626 subjects with OAB symptoms for at least 3 months were enrolled and randomized to treatment (202 to placebo, 210 to oxybutynin gel [56 mg/day], and 214 to oxybutynin gel [84 mg/day]). Of the 626 subjects that were randomized to the treatment groups in this study, 493 (79%) completed the 12-week double-blind period. A total of 133 subjects (21%) discontinued prematurely, primarily due to an adverse event (50 subjects [38%]). More patients exposed to oxybutynin gel discontinued because of an adverse event (9% in the 84 mg/day group and 10% in the 56 mg/day group compared to 5% in the placebo group), whereas more placebo patients discontinued because of patient decision not to participate further (see Table 2).

Table 2: Subject disposition for Study 20070060*

		Treatment Groups			Overall (%)
		Oxybutynin 84 mg (%)	Oxybutynin 56 mg (%)	Placebo (%)	
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)

*Adapted from the Clinical review, Table 9.

Efficacy Endpoints:

Primary endpoint:

- Change from baseline to week 12 in the number of urinary incontinence episodes per week as determined from a 3-day patient daily diary

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

- Average urinary frequency per day based on entries in the 3-day diary
- Average urinary void volume per void based on entries from 2 consecutive days in the 3- day patient diary

Comment: The efficacy endpoints were acceptable to the Clinical and Statistical review teams for the indication of treatment of overactive bladder (OAB).

Statistical Analyses:

The pivotal study reviewed by the statistical review team to determine the efficacy of the 56 mg and 84 mg Anturol doses was Study 20070060. As previously discussed, data from

subjects in this study who used the original formulation were combined with data from subjects using the to-be-marketed formulation. Due to the non-normality of the data for the change from baseline in the number of urinary incontinence episodes (UIE) at each visit, the reviewer's analyses were also based on the rank-transformed UIE data. 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 were 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.

Comment: The Statistical review team identified two key statistical issues of concern associated with the sponsor's statistical analysis of the primary efficacy data from Study 20070060 :

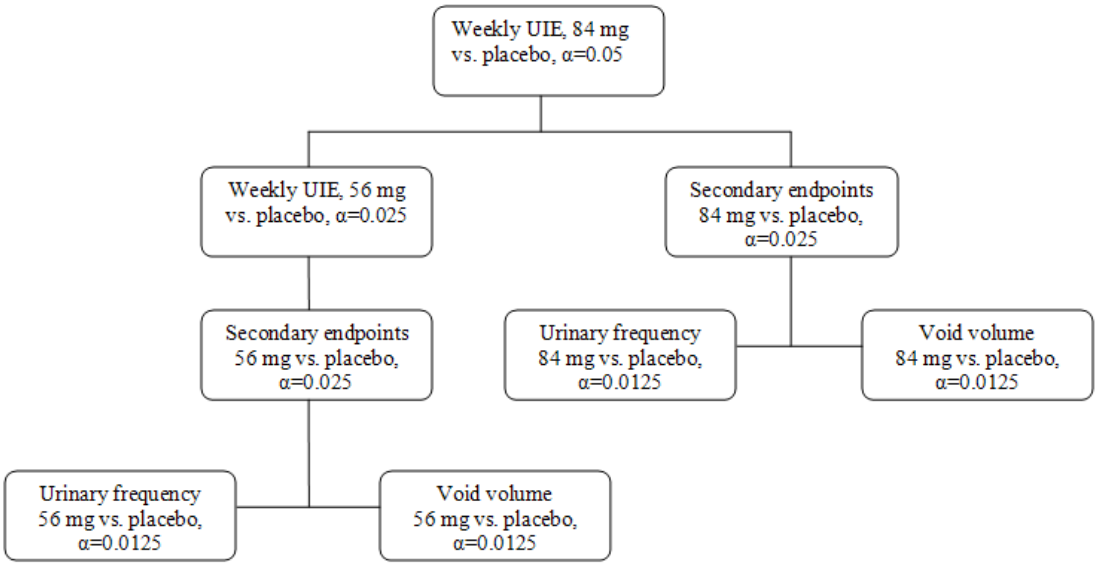
- *"The applicant provided two procedures to adjust for multiplicity in this application: one prespecified prior to data base lock and a modified version after the data base was unblinded….. This memo (containing the modified version) was dated as 08/24/2010 and the analysis results of unblinded data were discussed in it."*
- *"The applicant's primary analyses were based on the modified ITT population rather than the ITT population for the efficacy endpoints. The modified ITT population defined by the applicant may not represent the potential target population of this test drug."*

  (See Statistical review dated November 30, 2011).

The Statistical reviewer evaluated the sponsor's submission and determined that pre-specified testing analyses procedures outlined in the final statistical analysis plan (SAP) dated June 10, 2010 should be followed. The Clinical review team concurred with the Statistical reviewer's conclusion that the analyses as stated in the June, 2010, SAP should be followed to determine efficacy of this oxybutynin gel product.

The primary efficacy analysis outlined in the sponsor's final SAP is outlined in 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.

Comment: The sponsor confirmed that the testing sequence outlined above was the pre-specified sequence for Study 20070060 from the final statistical analysis plan dated June 10, 2010. The Statistical and Clinical reviewers concluded that the primary efficacy analyses for this application would be based on the June, 2010, statistical analysis plan proposed and finalized prior to unblinding. The Statistical reviewers also determined that the statistical analysis plan dated August 24, 2010 was considered a post-hoc change, and therefore, not acceptable for the purposes of conducting the primary efficacy analysis for this study.

Efficacy Results:

The primary and secondary efficacy analyses were based on the ITT population as described in the sponsor's final statistical analysis plan (signed June 10, 2010).

Primary efficacy analysis results for both the 84 mg and 56 mg doses are outlined in Table 3 below:

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

Weekly UIE	n	UIE 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: Adapted from the Statistical reviewer's analysis on ITT population, Table 8
[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

A brief summary of the primary efficacy analyses summarized from Table 3 includes:

- At the 84 mg dose, the median change from baseline to Week 12 in weekly UIEs was -16.4 episodes experienced by patients 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.

(b) (4)

Comment: The Statistical reviewer concluded in her November 30, 2011, review that, "Based on the protocol specified endpoints, i.e., the change from baseline in number of UIE, average daily urinary frequency, and average urinary volume per void to Week 12, the results of study 20070060 provided statistical evidence of efficacy for the higher dose of Anturol 84 mg/day, but not for the lower dose of Anturol 56 mg/day after adjusting for type I error by pre-specified multiplicity controlling method."

The Clinical reviewer concurred with the statistical reviewer's conclusions and also noted that, "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." (See Clinical review dated December 6, 2011)

Key secondary efficacy analysis for the 56 mg and 84 mg doses are outlined in Tables 4 and 5 below:

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

Average Daily Urinary Frequency	**n**	**Urinary frequency 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: Adapted from the Statistical reviewer's analysis on ITT population, Table 9

[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.

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

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

Source: Adapted from the Statistical reviewer's analysis on ITT population, Table 10

[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.

The secondary efficacy analyses as summarized in Tables 4 and 5:

- Compared to placebo, Anturol 84 mg/day showed statistically significant reductions for both secondary endpoints. The p value for the change in daily urinary frequency was <0.0010 and the p value for the change in average urinary void volume was <0.0001 at Week 12 (the pre-specified 0.0125 level, 2-sided);
- Compared to placebo, Anturol 56 mg/day failed to show statistically significant results for either secondary efficacy endpoint at Week 12.

Comment: The Statistical reviewer, in her review dated November 30, 2011, added that, [redacted]

The Clinical reviewer then concluded that, "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."(See Clinical review dated December 6, 2011)

I concur with the Statistical and Clinical review teams that only the 84 mg dose had confirmatory evidence of efficacy from a statistical perspective.

Summary of Efficacy:

The statistical reviewer summarized her conclusions in a review dated November 30, 2011 as follows:

"The results for 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 are as follows:

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

The Statistical reviewer concluded that, "The data in this application support the efficacy of Anturol 84 mg/day dose for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency. However, the data do not support the lower dose of Anturol gel 56 mg/day, because the evidence was not statistically significant, after adjusting for type I error per protocol specified multiplicity controlling method."

The Clinical reviewer concurred with the statistical reviewer's conclusions in a review, dated December 6, 2011, and added that, (b) (4)

The CDTL reviewer concurred with the Statistical and Clinical reviewers and concluded that, "….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." (See CDTL review dated December 6, 2011)

1. *I concur with the recommendations of the Statistical reviewer, Clinical reviewer and CDTL that there are no outstanding efficacy concerns for the new Anturol gel product at the 84 mg dose.*
2. *I also concur with the Clinical and Statistical reviewers that the 56 mg dose is NOT effective (superior to placebo) for the indication of treatment of OAB given the present efficacy data on the basis of the statistical results.* (b) (4)

8. Safety

The Clinical review team evaluated the safety database for this application. The sponsor submitted a total of 8 clinical studies in 826 subjects who received at least one dose of Anturol. Five of the eight studies used the to-be-marketed formulation, (b) (4)

including the majority of the subjects in the pivotal phase 3 trial (Study 20070060). A summary of the submitted studies that comprised the safety database is outlined in Table 6.

Table 6: Summary of submitted clinical studies*

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)		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	

*Adapted from the Clinical review, Table 5.

Several doses of oxybutynin gel, primarily containing the original formulation, were evaluated in the phase 1 and 2 studies. Therefore, the primary assessment of safety was based on Study 20070060, which used the to-be-marketed formulation (b) (4) 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 with placebo control.

Deaths and Nonfatal Serious Adverse Events:

Phase 1 and 2 studies: There were no deaths in the phase 1 and 2 studies or in the phase 3 trial (Study 20070060). In addition, there were no reported serious adverse events in the phase 1 and 2 studies.

Study 20070060: A total of nine subjects experienced at least 1 serious adverse event in the phase 3 trial.

Comment: The Clinical reviewer evaluated the serious adverse events in trial #20070060 and concluded that none of these serious adverse reactions were related to the study drug.

Dropouts and/or Discontinuations:

Phase 1 and 2 studies: There were no dropouts related to adverse reactions in the Phase 1 and 2 studies.

Study 20070060: A total of 50 subjects (8%) discontinued study drug due to treatment emergent adverse events, 10 subjects (5%) in the placebo arm and roughly 10% in each oxybutynin treatment group (9% and 10% for the 84 mg/day and 56 mg/day groups, respectively). 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 that resulted in discontinuation of study drug were reported as resolved.

Common Adverse Events:

Phase 1 and 2 studies: The Clinical review team determined that there was insufficient exposure to the to-be-marketed formulation in the Phase 1 and 2 clinical studies to provide a sufficient evaluation of common adverse events. Therefore, review of common adverse events focused primarily on those identified in the phase 3 trial. Additionally, the results from subjects using the original and to-be-marketed formulations were pooled.

Study 20070060: The most common adverse reactions in the subjects treated with oxybutynin gel in the Phase 3 trial were dry mouth (12%), application site erythema (3.7%), constipation (3.7%), application site rash (3.3%) and are outlined in Table 7 below:

Table 7: Common adverse reactions in Study 20070060 (≥ 2% and > placebo)*

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: Adapted from the Clinical review, Table 17.

The Clinical review team also evaluated both the adverse reactions reported for the phase 3 trial specifically related to the anti-muscarinic effects (also termed anticholinergic) of this class of medications (dry mouth, constipation, blurred vision, urinary retention and urinary tract infection). The Clinical reviewer's summary of these anticholinergic adverse events is outlined in Table 8 below:

Table 8: Anticholinergic adverse reactions reported for subjects in Study 20070060.

	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		

*Source: Adapted from the Clinical review, Table 15.

Comment: The Clinical reviewer stated in his review dated December 6, 2011, that, "There was a dose relationship of some of the anticholinergic related adverse reactions such as constipation and dry mouth…. 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."

I concur with this assessment.

Laboratory Findings

Phase 1 and 2 studies: The Clinical review team determined that there were insufficient laboratory data in the Phase 1 and 2 clinical studies to provide a sufficient evaluation.

Therefore, review of laboratory findings focused primarily on those identified in the phase 3 trial.

Study 20070060: The clinical reviewer did not identify any clinically significant treatment-related adverse changes in laboratory safety parameters. Mean values for hematology and biochemistry variables remained within respective normal ranges throughout. There were no obvious trends in regard to differences in hematology or chemistry values between treatment groups.

Comment: The Clinical reviewer evaluated the laboratory findings from Study 20070060 and concluded that, "There were no significant treatment-related adverse changes in laboratory safety parameters." (See Clinical review dated December 6, 2011)

I concur with the Clinical reviewer's assessment of the laboratory data and concur that there are no outstanding safety issues related to laboratory findings.

Application site reaction data collected from the phase 3 study:

Phase 3 trial (20070060): The types and numbers of subjects with application site reactions were collected through routine adverse event reporting and divided into the following categories; erythema, rash, pruritus, irritation, and reaction. All of the application site reactions were numerically higher for drug than placebo (See Medical officer's review, table 16). The percentage of subjects experiencing at least one form of application reaction was roughly equivalent amongst the two doses. The number of subjects with application site reactions of any kind were significantly more common for active drug (both dosages combined) than placebo ($p<0.0008$).

Comment: The Clinical reviewer performed an analysis of the effect of application site reactions and whether the change of formulation (b) (4) *altered the rate of application site reaction. He also reviewed the open-label extension study of Study 20070060 for skin tolerance. After review of these application site reactions, the Clinical reviewer concluded that, "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 the application site reactions reported with the to-be-marketed formulation." (See Clinical review dated December 6, 2011)*

The CDTL leader further commented on the application site reactions in his review dated December 6, 2011, that, "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."

I concur with the assessments of the Clinical reviewer and CDTL that the reported application site reactions can be addressed through product labeling.

Other key safety studies:

[redacted] (b) (4) the Division determined that results from the phase 1 studies related to sunscreen interaction, showering and transfer to others were not applicable to the new formulation and needed to be repeated. These four studies were outlined in the Clinical Pharmacology section (Section 5) of this review.

In addition, an open-label extension study that included subjects who had completed the primary phase 3 trial (Study 20070060) was conducted.

1. Open label skin tolerance extension study (20070060 OLE)

An open-label extension study was conducted in subjects who had completed Study 20070060 to provide additional safety data. The study duration was 24 weeks and all subjects received the 84 mg dose of the to-be-marketed formulation. A total of 77 subjects entered the open-label extension, with 63 (82%) completing 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 nine subjects (12%) and three of these subjects dropped out of the study. Other frequent treatment emergent adverse events were urinary tract infections and nasopharyngitis, roughly 5% each.

Comment: The results of the phase 1 studies (showering, sunscreen application and transfer) using the to-be-marketed formulation were reviewed by the Clinical Pharmacology and Clinical review teams. No new safety signals were identified. The results of these studies are addressed in labeling as appropriate.

Safety summary:

The phase 3 trial (Study 20070060) has demonstrated that the 84 mg/day oxybutynin gel product has a safety profile that appears to be similar to other available oxybutynin products.

There were no deaths in Study 20070060 and no serious adverse events that appeared to be drug-related. The dropouts and discontinuations for adverse reactions of the to-be-marketed oxybutynin drug product appear to be consistent to those seen with other anticholinergic products. The common adverse events reported in Study 20070060 were dry mouth (12%), application site erythema (3.7%), constipation (3.7%), and application site rash (3.3%). Finally, there were no reports of severe application site reactions following any application in Study 20070060.

The potential safety issues of application site reactions and unintentional secondary exposure to others can be addressed in product labeling.

The Clinical reviewer stated that, "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. ….. 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." (See Clinical review dated December 6, 2011)

The cross-discipline team leader (CDTL) concurred with the primary medical officer's recommendation in his CDTL review (dated December 6, 2011) and concluded that, "No significant safety issues for either dose (56 mg or 84 mg) were detected."

Comment: I concur with the recommendations of the Clinical reviewer and CDTL that there are no outstanding safety issues for this application.

9. Advisory Committee Meeting

Oxybutynin was first approved in tablet form in 1975. A transdermal patch containing oxybutynin (Oxytrol TDS) was approved in 2003 and a topically applied gel containing oxybutynin (Gelnique) was approved in 2009. The efficacy of this oxybutynin gel product appears to be comparable to the other approved drugs in its class and no new safety concerns were identified during the review. No advisory committee was convened.

10. Pediatrics

The sponsor requested a full waiver for a pediatric assessment for all pediatric age groups.

A full waiver was granted for Anturol because it does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not expected to be used in a substantial number of pediatric patients.

11. Other Relevant Regulatory Issues

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Patient Package Insert (PPI) and completed their review on November 2, 2011. Their recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information, the PPI, and the Dear Healthcare Provider Letter and completed their review on November 2, 2011. Their recommendations were implemented.

Office of Scientific Investigations (OSI):

There were no OSI audits or inspections requested for this application.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team determined that the proprietary name of Anturol was acceptable on July 29, 2011.

The DMEPA review team reviewed the carton and container labels, labeling, and the DHCP letter and made recommendations to the FPI and carton/container labeling (See DMEPA review dated October 21, 2011). These recommendations were implemented.

Financial Disclosure**:**

Financial disclosure information was submitted for the clinical investigators (principal and sub-investigators) for the phase 3 trial (Study 20070060, which was the primary study reviewed for approval). No financial conflicts were reported.

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team concluded in a review finalized on December 1, 2011, that the final labeling was acceptable.

12. Labeling

Labeling negotiations are complete and there are no outstanding labeling issues.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the cross-discipline team leader (CDTL), Clinical, Clinical Pharmacology, Pharmacology/Toxicology, CMC, and Statistical reviewers that Anturol (oxybutynin chloride) gel at a dose of 84 mg daily should be approved.

(b) (4)

Risk Benefit Assessment:

The results of the single, placebo controlled trial 20070060 demonstrated that Anturol treatment at the 84 mg dose resulted in statistically significant improvement in the primary endpoint (urinary incontinence episodes) and the key secondary endpoints (urinary frequency and urine volume per void) compared to placebo at 12 weeks. Although no adequately designed trials have compared the efficacy of Anturol to other

approved anticholinergic drugs for the treatment of OAB, the efficacy results seen with Anturol appear to be similar. Supportive PK data demonstrate that the AUC, C_{avg}, and C_{max} values for oxybutynin and desethyloxybutynin are similar for Anturol and Oxytrol.

The safety profile of Anturol at the 84 mg dose is acceptable. The expected anticholinergic adverse reactions of a transdermally applied oxybutynin product that were seen in Trial 20070060 can be adequately labeled. Application site reactions that were reported were included in the ADVERSE REACTIONS section of labeling as appropriate. The potential risk of transference to others that was identified in the person-to-person transfer study (SCO 5486) has been clearly outlined in the WARNINGS and PRECAUTIONS section (5.3) and instructions for prevention of transference are in the PATIENT COUNSELING INFORMATION section (17.1).

The benefit/risk evaluation favors approval of Anturol at the 84 mg dose. I agree with the Clinical, CMC, Pharmacology/Toxicology, Clinical Pharmacology and Statistical reviewers as well as the CDTL, that NDA 202-513 should be approved at the 84 mg dose. Label negotiations are completed. No postmarketing studies are necessary.

There are no outstanding issues regarding approval of this NDA for Anturol at the proposed 84 mg dose.

The results of the single, placebo controlled trial 20070060 demonstrated that Anturol treatment at the 56 mg dose did NOT result in a statistically significant improvement in the primary endpoint (urinary incontinence episodes). Key secondary endpoints (urinary frequency and urine volume per void) for the 56 mg dose were also not statistically significant when compared to placebo at 12 weeks.

(b) (4)

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

None.

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/s/

AUDREY L GASSMAN
12/07/2011