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APPLICATION NUMBER:
202513Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Addendum (December 7, 2011) Clinical Pharmacology Review

NDA: 202513

Dates of Submission: December 17, 2010 (cover letter)
(Original submission)
Electronic: December 21, 2010
March 4, 2011 (Cover letter)
Electronic (March 10, 2011)
April 1, 2011 (cover letter)
Electronic (April 5, 2011)
April 21, 2011 (cover letter)
Electronic (April 21, 2011)

Electronic Document #: 1, 3, 4, 5,

Generic Name: Oxybutynin 3% Gel
Brand Name: Anturol®
Formulation: Transdermal
Strength: 3%

OCP Division: Division of Clinical Pharmacology III
OND Division: Division of Reproductive and Urologic Products
Route of Administration: Transdermal
Indication: Treatment of Overactive Bladder
Dosage and Administration: Once daily to abdomen, upper, arms/shoulders or
tights

Proposed Administration: (b) (4) three pumps (84 mg/day) (b) (4)

Application sites may be rotated to reduce the potential for local site reactions.

Type of Submission: Original NDA
Sponsor: Antares Pharma, Ewing, NJ
Reviewer: Sayed (Sam) Al Habet, R.Ph., Ph.D.

This is a short addendum to the clinical pharmacology review dated October 13, 2011. In page 3 of this review under Section 1.1 (Recommendation) it was indicated that the NDA is acceptable from the clinical pharmacology perspective provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant. As the time of writing this memo, the final labeling version submitted by the sponsor is acceptable from the clinical pharmacology perspective. Therefore, no further action is indicated at this time.

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/s/

SAYED AL HABET
12/07/2011

REV-CLINPHARM-02 (Review Noted (NAI))
NDA-202513
ORIG-1
Supporting Document 1
New/NDA
Submit Date: 12/20/2010 - FDA Received Date: 12/20/2010

ORIG-1
Supporting Document 3
Clinical/Clinical Information
Submit Date: 03/04/2011 - FDA Received Date: 03/04/2011

ORIG-1
Supporting Document 17
Labeling/Package Insert Final
Labeling/Container-Carton Final
Submit Date: 12/01/2011 - FDA Received Date: 12/01/2011

This is a short addendum to the clinical pharmacology review dated October 13, 2011. In page 3 of this review under Section 1.1 (Recommendation) it was indicated that the NDA is acceptable from the clinical pharmacology perspective provided that a mutually acceptable agreement regarding the labeling language can be reached between the Agency and the Applicant. As the time of writing this memo, the final labeling version submitted by the sponsor is acceptable from the clinical pharmacology perspective. Therefore, no further action is indicated at this time.

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/s/

SAYED AL HABET
12/05/2011

ONDQA (Biopharmaceutics) Review Addendum

NDA: 202-513 (3rd Review)
Submission Date: 7/22/11; 10/14/2011; 11/02/11; 11/07/11; 11/09/11
Product: Oxybutynin Gel, 3% (Anturol)
Type of Submission: Original NDA
Applicant: Antares Pharma, Inc.
Reviewer: Tapash K. Ghosh, Ph.D.

Regulatory History:

Reference is made to Antares Pharma Inc.'s original NDA 202-513 submitted to FDA on December 20, 2010, and received for review by FDA on February 8, 2011. During the review of the submission, several questions were sent to the Applicant in an Information Request (IR) Letter dated July 15, 2011. The Applicant responded to these questions in a submission dated July 22, 2011. Based on the provided information, the first Biopharmaceutics review for this submission was entered in DARRT on October 6, 2011. However, the review included several questions, which were conveyed to the Applicant on October 7, 2011. The Applicant responded to them on October 22, 2011. Further communications between the Applicant and FDA occurred via e-mail and t-con and 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:

Test	Method	Release and Stability Acceptance criteria
Release Rate		(b) (4)



The above acceptance criteria for the *in vitro* "Release Rate Test" will be implemented on an "*interim basis*" for one year. The Applicant 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, Antares Pharma submitted the official document attesting the following:

The Agency proposes an interim specification of (b) (4) for both release and stability. Further, once ten (10) commercial batches are manufactured, data should be submitted so that a final specification can be set. Antares Pharma accepted the Agency's proposal. 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:



Recommendation:

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.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer

Signed by Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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/s/

TAPASH K GHOSH
11/15/2011

ANGELICA DORANTES
11/15/2011

ONDQA (Biopharmaceutics) Review

NDA: 202-513 (2nd Review)
Submission Date: 7/22/11; 10/14/2011; 11/02/11; 11/07/11
Product: Oxybutynin Gel, 3% (Anturol)
Type of Submission: Original NDA
Applicant: Antares Pharma, Inc.
Reviewer: Tapash K. Ghosh, Ph.D.

Regulatory History:

Reference is made to Antares Pharma Inc.'s original NDA 202-513 submitted to FDA on December 20, 2010, and received for review by FDA on February 8, 2011. During the review of the submission, several questions were sent to the Applicant in an Information Request (IR) Letter dated July 15, 2011. The Applicant responded to these questions in a submission dated July 22, 2011. Based on the provided information, the first Biopharmaceutics review for this submission was entered in DARRT on October 6, 2011. However, the review included several questions, which were conveyed to the Applicant on October 7, 2011. The Applicant responded to them on October 22, 2011. Further communications between the Applicant and FDA occurred via e-mail and t-con and 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:

Test	Method	Release and Stability Acceptance criteria
Release Rate		(b) (4)



The above acceptance criteria for the *in vitro* "Release Rate Test" will be implemented on an "*interim basis*" for one year. The Applicant 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.

Recommendation:

ONDQA-Biopharmaceutics evaluated the information provided as of November 7, 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 with the following Post Marketing Commitment.

Post Marketing Commitment:

- 1. “Antares Pharma agrees to the Post Marketing Commitment (PMC) to collect and submit additional in vitro drug Release Rate data from at least ten (10) commercial batches of ANTUROLOL Gel 3%. These data will be used to set the final regulatory acceptance criteria for the Release Rate test of Anturol Gel 3%. To fulfill the PMC, within 12 months from approval date, a supplement to the NDA with the additional release rate data and a proposal for the final acceptance criteria for the “Release Rate” test will be submitted to the Agency”. Specifics of the PMC will be crafted later and sent along with the approval letter.*

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer

Signed by Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

Previous Relevant Communications between the Agency and the Applicant

➤ **Information Request dated July 15th and Applicant Response dated July 22nd:**

During the review of this NDA, the following questions were sent to the Applicant in an Information Request (IR) Letter dated 7/15/2011:

Submit the full development report for the proposed drug release (diffusion) test (method (b) (4)). The report should specifically describe the justification (s) for each of the following:



The Applicant responded to the IR in their correspondence dated July 22, 2011 (SN0008) as described and reviewed below.

Applicant's Response: As requested, the full development report for the drug release (diffusion) method (b) (4) is provided. Contained therein are the scientific rationale and the results from the studies that address the justification for the listed points.





Reviewer's comments: *The Applicant's response is acceptable.*

➤ **Information Request dated Oct 7th and Applicant Response dated Oct 22nd:**

During the review of the report, the following issues were identified and another IR Letter was drafted and sent out to the Applicant on October 7, 2011. The Applicant responded on October 22, 2011. The following section describes the Agency's request, the Applicant's response and the Agency's evaluation:

1. *Please submit the raw data (in electronic format) from each cell at each time point used to calculate slope (diffusion rate) for each formulation at different time in the stability protocol.*

Reviewer's Comment: *The response is acceptable.*

2. Clearly describe the method and associated data used to calculate slope and RSD values used in Table 1 and Table 2 in the Statistical Specifications Calculation. Also, clarify your intent (how and why) to use the "Diffusion Rate: RSD" as part of your release and stability specifications.

Reviewer's Comments: *The Applicant submitted the data in their October 22 and November 02, 2011 submissions. They proposed the deletion of the acceptance criteria from the Drug Product Specification for release and stability. However, they will maintain the limit within the analytical method [REDACTED] ^{(b) (4)} **The response is acceptable.***

3. Explain how you came up with "a priori" acceptance criteria for slope and RSD values.

Applicant's Response: *The acceptance criteria for the Release Rate: Slope and RSD were established based on analytical results acquired from ANTUROL drug product lots utilized in clinical and stability studies as described below:*

Response Item #3, Table 1: ANTUROL Finished Drug Product Lots Used in Setting Drug Product Release and Stability Specifications

Where Used	Finished Product Lot/Batch Number						
	HKB	HKC	KHV	KHW	R0266B003	Oxyg223-03B/P1	Oxyg223-05B/P1
Supportive Lot/Batch Stability						X	X
Registration Lot/Batch Stability	X	X	X	X	X		
Clinical Studies	X ¹				X ¹		X ²

¹Pivotal Phase III

²Bioequivalence study comparing (b) (4) and (b) (4) formulae

Reviewer's Comment: The response is acceptable.

4. (b) (4) and stability (b) (4) That is not what the Agency agrees upon. We recommend that you calculate the ranges based on Mean \pm 90% CI (confidence interval) data.



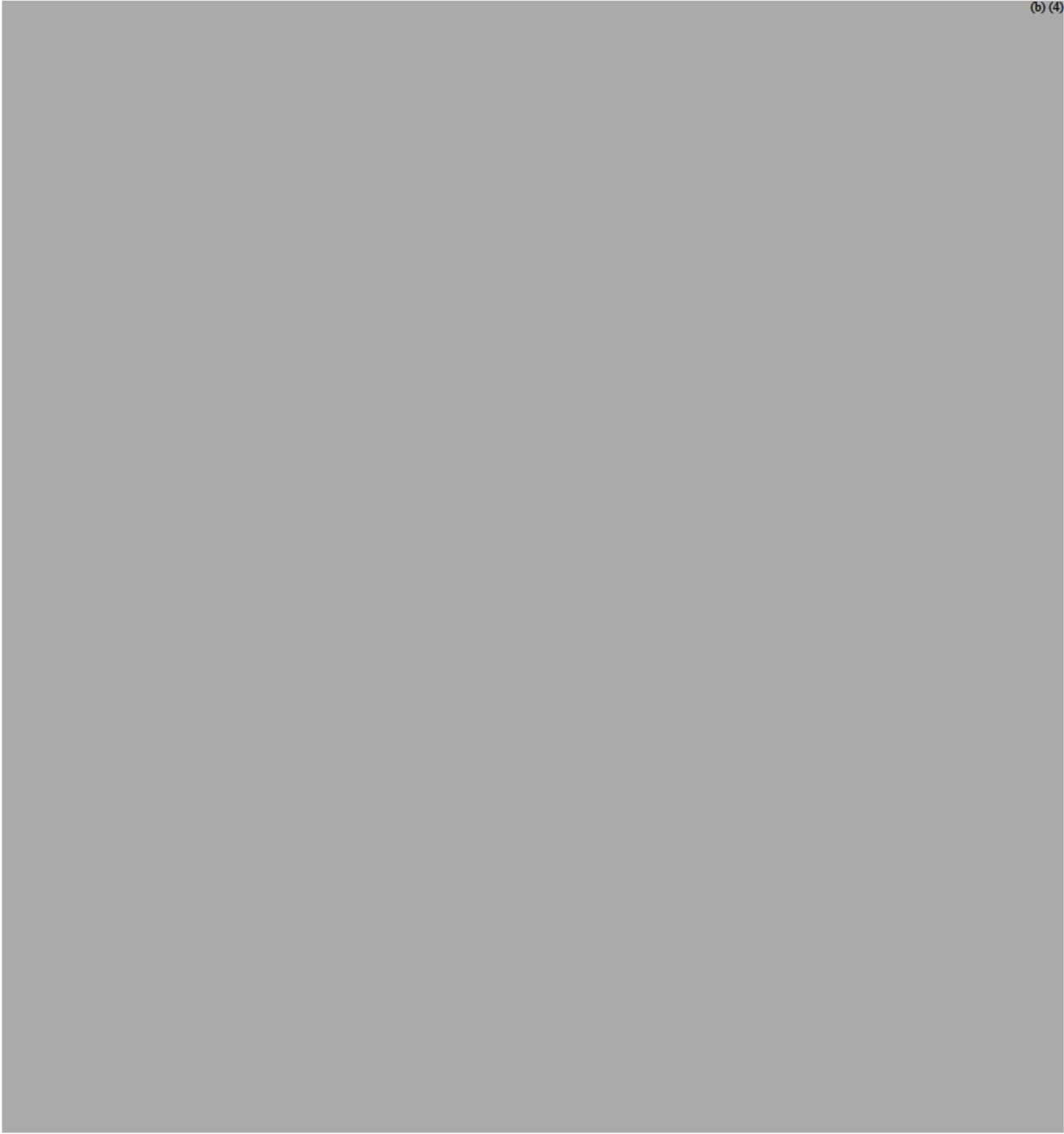
(b) (4)

Based on the fact that currently the Applicant has a limited number of batches, their database is not yet large and establishing the acceptance criteria for the release rate test based on a 90% confidence interval alone is limited. The Applicant proposed to (b) (4)

(b) (4) for stability we propose (b) (4) from the current limits of (b) (4) to (b) (4)

Response Item 4, Attachment 3

NDA 202-513, SN0012



(b) (4)

(b) (4)



Reviewer's Comments: *The Applicant's response and their proposal for the release rate acceptance criteria were not acceptable. Based on the Applicant's response, the reviewer created the following Tables using JMP 9.0.2 version.*

Table: Statistical Parameters on Release Data

Batch	Release Rate (Slope)	90% Confidence Interval	
		Lower	Upper
	(b) (4)		
HKB			
HKC			
KHV			
KHW			
Oxyg22303			
Oxyg22305			
R0266B003			
Mean		(b) (4)	
SD			

Table: Statistical Parameters on Stability Data

Release Rate (Slope)		90% Confidence Interval	
Mean	SD	Lower	Upper
(b) (4)			

Based on the outcome of the Reviewer’s analysis, the Applicant was told in a t-con on 11/02/2011 that the Agency’s proposal for the Release Rate was (b) (4) both at release and stability.

5. Please designate the “Slope” values as “Release Rate” in your product specifications.

Applicant’s Response: The Applicant agreed to designate the slope value as the in vitro drug release rate.

Reviewer’s Comment: The response is acceptable.

6. Please explain why the value of slope (b) (4) for the batch “HKC” as submitted in the original submission is different (b) (4) in the amendment submitted on 8/5/11 in Table 41.

Applicant’s Response: The Applicant acknowledges that as typographical error and corrected it. In response to FDA comment 6, all tables and results reports in Sections 3.2.P.8.1 and 3.2.P.8.3 have been audited and determined to be correct.

Reviewer’s Comment: The response is acceptable.

7. In your stability report – 2011-001 Ver. 00 signed on 8/2/11, on Page 65 under section 7.9, you quoted “There are, however, obvious inter-batch differences. The batch pairs HKB/KHV and HKC/KHW have Release rates that are significantly different (b) (4) (b) (4)”.

Please explain what *in-vivo* data you have to assure that product batches with such different viscosities and release rates will have similar *in-vivo* performance (e.g., bioavailability, efficacy and safety). Also, explain what steps you plan to take to control grades of (b) (4) to be used in your commercial product batches to have a tighter control of your product quality and performance.

Applicant’s Response: Phase III clinical trials were carried out with the following product batches:

- C0847B001 (b) (4)
- R0266B003 (b) (4)

- HKB (b) (4)

Batch CO847B001 (b) (4) was the initial batch used in the Phase III clinical trial. After the Phase III trial was started, the formulation was changed (b) (4) and with the Agency's concurrence, the trial was continued using batches R0266B003 and HKB, (b) (4) and represent the Anturool drug product to be commercialized. The supporting evidence (b) (4) was obtained by demonstrating bioequivalence (BE) of the two formulations in a BE study (SCO5432). The batches used in the BE study were:

- Oxyg146-20B/P1 (b) (4)
- Oxyg223-05B/P1 (b) (4)

Since it was shown that the (b) (4) formulations are bioequivalent, and both (b) (4) were used in the Phase III trials, the viscosity and the release rate characteristics intrinsic to these batches used in the successful BE and Phase III clinical trials represent the minimum range of viscosity and release rate (Slope) values that will support bioavailability, efficacy and safety. In Table 1 below, the viscosities and diffusion rates for the above cited batches are presented.

Response Item #7, Table 1: Viscosity and Diffusion Rate

Batch	Viscosity (cP)	Slope of Diffusion Rate (b) (4)
CO847B001	(b) (4)	(b) (4)
R0266B003	(b) (4)	(b) (4)
HKB	(b) (4)	(b) (4)
Oxyg146-20B/P1	(b) (4)	(b) (4)
Oxyg223-05B/P1	(b) (4)	(b) (4)

Reviewer's Comments: Overall, the Applicant's response is acceptable. However, the following comments should be noted:

- The Applicant's statement that batches Oxyg146-20B/P1 (b) (4) and Oxyg223-05B/P1 (b) (4) were bioequivalent is not true. However, the Office of Clinical Pharmacology (OCP) accepted the results based on other evidence and that is fine with this reviewer (See OCP's review in DARRT).

- Table 1 above demonstrates that Viscosity and Release (Diffusion) Rates (b) (4)

➤ **T-con dated Nov 2nd and Applicant Response dated Nov 4th:**

In response to the t-con with the Applicant on 11/02/11, the Applicant responded on 11/04/11 reinstating that they believe a release rate specification of (b)(4) is justifiable based on their data. Upon further review of the data, the Agency proposed a final proposal of a release rate specification of (b)(4) for both release and stability. Once 10 commercial batches are manufactured, data should be submitted so that a final specification can be set.

On 11/07/11 via e-mail, the Applicant accepted the Agency's recommendation of establishing on an interim basis the Release (Diffusion) Rate acceptance criteria limits of (b)(4) for batch Release and Stability testing (Shelf-life) for ANTUROL finished product.

Once Antares has produced and analyzed ten (10) commercial batches of ANTUROL Gel 3%, the Release Rate acceptance criteria limits will be re-assessed based on these data and along with final specification limits will be submitted as a Post Marketing Commitment under a Supplement to the NDA.

Reviewer's Comments: The Applicant's proposal is acceptable.

OVERALL ASSESSMENT:

2. The optimized in vitro drug release (diffusion) method and acceptance criteria (on interim basis) for the evaluation of Anturool (oxybutynin Gel, 3%) are described below:



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

3. Antares Pharma agreed to collect and provide additional “Release Rate” data from ten (10) commercial batches of ANTUROL Gel 3% as a Post Marketing Commitment (PMC). These data will be used to set the final “Release Rate” acceptance criteria limits. To fulfill the PMC, these data along with a proposal for the final criteria limits will be provided under a supplement to the NDA within 12 months from NDA’s approval date. Specifics of the PMC will be crafted later and sent along with the approval letter.

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/s/

TAPASH K GHOSH
11/08/2011

ANGELICA DORANTES
11/08/2011

Final (October 13, 2011) Clinical Pharmacology Review

NDA: 202513

Dates of Submission: December 17, 2010 (cover letter)
(Original submission)
Electronic: December 21, 2010
March 4, 2011 (Cover letter)
Electronic (March 10, 2011)
April 1, 2011 (cover letter)
Electronic (April 5, 2011)
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Electronic Document #: 1, 3, 4, 5,

Generic Name	Oxybutynin 3% Gel
Brand Name:	Anturol®
Formulation:	Transdermal
Strength:	3%
OCP Division:	Division of Clinical Pharmacology III
OND Division:	Division of Reproductive and Urologic Products
Route of Administration:	Transdermal
Indication:	Treatment of Overactive Bladder
Dosage and Administration:	Once daily to abdomen, upper, arms/shoulders or tights
Proposed Administration:	(b) (4) three pumps (84 mg/day) (b) (4)
	Application sites may be rotated to reduce the potential for local site reactions.
Type of Submission:	Original NDA
Sponsor:	Antares Pharma, Ewing, NJ
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

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1.0 Executive Summary

Oxybutynin is an antispasmodic, antimuscarinic agent. It exists as racemic mixture of R and S-isomers. Oxybutynin was first approved in 1975 for the treatment of overactive bladder under the trade name, Ditropan® IR tablet. Other products followed such as Ditropan XL tablet, syrup, and topical gel (Gelnique®), and transdermal patches (Oxytrol®).

The current gel is a transparent, fast-drying, colorless to slightly yellow, non-occlusive containing 3.0% w/w oxybutynin free base. The product will be supplied in a metered-dose pump delivering 28 mg of oxybutynin per actuation. The proposed dosage of the product is [REDACTED]^{(b) (4)} 84 mg (3 actuations) daily alternating among three sites: upper arm/shoulders, abdomen, and thighs.

1.1 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.

1.2 Phase 4 Commitment/Requirement

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

1.3 Summary of Important Clinical Pharmacology Findings:

This is a 505(b) (2) application for 3% gel containing oxybutynin packaged in a plastic container with a metered-dose pump for delivery. Briefly, in addition to the double blind placebo controlled safety and efficacy study in approximately 600 patients at two doses of 56 mg and 84 mg for 12 weeks (Study # 2007/0060), the sponsor conducted the following clinical pharmacology studies:

- Pilot study (2 gram vs 1 gram gel per day x 7 days (Study # OXPK2)
- Multiple dose (dose escalation) study at the following doses: 42 mg, 60 mg, and 84 mg per day (QAM) x 20 days (pivotal PK study # 1034-PhII)
- Bioequivalence (BE) for bridging the old formulation [REDACTED]^{(b) (4)} and the to-be-marketed (TBM) formulation [REDACTED]^{(b) (4)} (Study # SCO 5432)
- Effect of application site on the absorption of oxybutynin (abdomen, thighs, and arms/shoulders (Study # OXBTN/2006/223)
- Investigating partner-to-partner transfer of oxybutynin (i.e., skin-to-skin contact, Study # SCO 5486)
- Effect of showering on oxybutynin plasma concentration (Study # SCO 5488)
- Effect of sunscreen on the absorption of oxybutynin (Study # SCO 5487)
- *Ex Vivo* skin penetration study with the old formulation [REDACTED]^{(b) (4)} and the TBM formulation [REDACTED]^{(b) (4)} (Study # 368/03)

Summary of Clinical Pharmacology Program:

The Phase III and the TBM Formulations

During Phase III study, it was discovered that (b) (4) (b) (4). Therefore, the sponsor modified the formulation (b) (4) during Phase III study after 130 patients have been studied (b) (4). The new formulation (b) (4) was used in 496 patients to complete Phase III study. Therefore, a bridging study was necessary between the two formulations.

It should be noted that the pilot, dose escalation, and application site studies were conducted with (b) (4) formulation, whereas the transfer and sunscreen studies were conducted with the formulation (b) (4).

The BE Results of the Phase III and the 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 was 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 1.3.1).

Table 1.3.1. 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 _{1/2}	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 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.

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 (see Medical Officer's review).

Dose-Exposure Relationship

The dose escalating study was conducted to evaluate a single-dose and multiple-dose PK and safety profiles in 48 healthy males and females at three doses: 42 mg, 60 mg and 84 mg/day for 20 days (Study 1034-PhII). There was an increase in exposure with doses (42, 60, and 84 mg) for both oxybutynin and its active metabolite. The mean C_{max} 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 showed that the C_{max} did not increase substantially after the 20th dose.

Effect of Application Site

The effect of 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, reference site), site B (inner and upper part of 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%. 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.

Partner-to-Partner Transfer of Oxybutynin

The partner 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 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 one that had one measurable concentration of 0.06 ng/mL (just above the LOQ of the assay of 0.05 ng/mL).

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.

There was no evidence of effect of sunscreen on the absorption of oxybutynin when it was applied 30 minutes before or 30 minutes after oxybutynin 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 wash 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 treatments. 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.

From this study it can be concluded that showering at 1, 2, or 6 hours after application of the gel has no effect on the absorption of oxybutynin.

Pediatric Waiver Request:

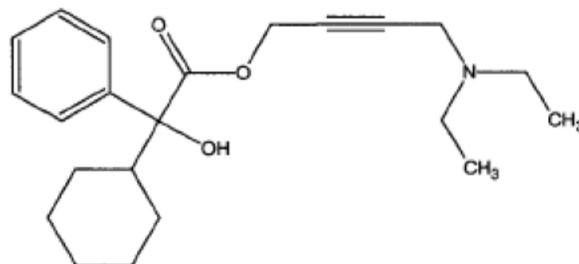
The sponsor is requesting waiver for pediatric studies with 3% oxybutynin gel. This is due to the availability of therapeutic alternatives in pediatric patients. Ditropan XL for example is approved in 5 years and older. However, transdermal products Oxytrol® and Gelnique® gel are approved for use in adults only. This request will be discussed separately at the PeRC meeting.

2. Question Based Review

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Oxybutynin is an antispasmodic, antimuscarinic agent. It exists as racemic mixture of R- and S-isomers. Its empirical formula is C₂₂H₃₁NO₃ and its structural formula is as follows:



Oxybutynin is a white powder with a molecular weight of 357.

The gel is a transparent, fast-drying, colorless to slightly yellow, non-occlusive containing 3.0% w/w oxybutynin free base. The product is a homogeneous gel, without particles.

The composition of the drug product, the quality standard and the function of each constituent of the drug product are presented in **Tables 2.1.1.1 and 2.1.1.2**.

Table 2.1.1.1 Components of Oxybutynin 3% Gel

Component and Grade	Regulatory/Safety Status	Function
Oxybutynin base	US DMF	Active Ingredient
Diethylene glycol monoethyl ether, NF (DGME)	USP/NF	(b) (4)
(b) (4)	USP/NF	
Hydroxypropyl cellulose (b) (4) NF	USP/NF	
Propylene glycol, USP	USP/NF	
Butylated hydroxytoluene, NF	USP/NF	
HCl 0.1 M	USP/NF	
Purified water, USP	USP/NF	

Table 2.1.1.2 Concentration of Components in Oxybutynin Gel 3%

Ingredient	Oxybutynin Gel Concentration (% w/w)	Oxybutynin Gel Concentration (mg/g)	Maximum value from IIG for topical or transdermal
Oxybutynin	3.00	30.0	N/A
Diethylene glycol monoethyl ether, NF (DGME) ¹	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl cellulose, NF	(b) (4)	(b) (4)	(b) (4)
Propylene glycol, USP	(b) (4)	(b) (4)	(b) (4)
Butylated hydroxytoluene, NF	(b) (4)	(b) (4)	(b) (4)
HCl 0.1 M	(b) (4)	(b) (4)	(b) (4)
Purified water, USP	(b) (4)	(b) (4)	(b) (4)

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

as shown in **Table 2.1.1.3**. 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.

Table 2.1.1.3. Description and Composition of Oxybutynin Gel (b) (4)

Component and Grade	Phase 3 Concentration Modified Formulation (%w/w)	Pre Phase 3 Concentration Original Formulation (%w/w)	Function
Oxybutynin base	3.00	3.00	Active Ingredient
Diethylene glycol monoethyl ether, NF	(b) (4)	(b) (4)	(b) (4)
Hydroxypropyl cellulose	(b) (4)	(b) (4)	(b) (4)

Propylene glycol, USP	(b) (4)
(b) (4)	
Butylated hydroxytoluene, NF	
HCl 0.1 M (b) (4)	
Purified water, USP	

(b) (4)

How Supplied

The product will be supplied in a metered-dose pump dispenser as follows:

- 2 X (b) (4) metered pump dispensers each containing 30 metered 0.92 g (1.0 mL) pumps delivering 28 mg oxybutynin per pump actuation.
- (b) (4) metered pump dispenser containing 90 metered 0.92 g (1.0 mL) pumps delivering 28 mg oxybutynin per pump actuation.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.2.1 Mechanism of Action:

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

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

2.1.2.2 Indication:

The proposed indication is the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended (b) (4) dosage is (b) (4) three pumps of gel ((b) (4) 84 mg/day) applied once daily to clean, dry, intact skin on the abdomen, or upper arms/shoulders, or thighs. (b) (4)

(b) (4) Application sites may be rotated to reduce the potential for local site reactions.

2.1.4 What are the core studies submitted in this NDA?

From the clinical pharmacology perspective, the sponsor conducted 6 major clinical pharmacology studies and three ex-vivo skin penetration studies. The first is BE study to bridge the old formulation (b) (4) and the new formulation (b) (4) (Study SCO 5432). The second study is the effect of site of application where the sponsor is proposing that patients should alternate the application sites of the gel (Study # OXBTN/2006/223). The third is Phase II dose ranging study that was used to determine the doses to be used in Phase III study (Study # 1034-Phase II). These studies among other studies will be discussed in more details in the subsequent sections of this review.

2.2 General Clinical Pharmacology

2.2.1 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

Efficacy:

In Phase III study, the Sponsor conducted a single, double-blind, randomized, 12-week clinical trial comparing the effects of 2 doses of the gel (containing 56 and 84 mg oxybutynin base) to placebo in patients with urinary frequency urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes. The primary endpoint in this study was the change from Baseline to Week 12 in the numbers of urinary incontinence episodes (UIE) per week (**Figure 2.2.1.1**). This is determined from a 3-day patient daily diary.

Figure 2.2.1.1. Median Change from Baseline in Number of Urinary Incontinence Episodes Per Week During 12-Week Double-Blind Treatment Periods (modified Intent-to-Treat Population)



Table 2.2.1.1. Baseline and Changes in Weekly Urinary Incontinence Episodes: Comparison of Oxybutynin Gel and Oxytrol-TDS

	Anturol Study 20070060			Oxytrol Study 1	
	Placebo (n = 166)	56 mg/day (n = 171)	84 mg/day (n = 195)	Placebo (n = 127)	39 mg/day (n = 120)
Baseline number of Weekly Urinary Incontinence Episodes					
Mean (SD)	45.8 (28.85)	(b) (4)	43.6 (27.50)	37.7 (24.0)	34.3 (18.2)
Median	42.0	(b) (4)	37.3	30	31
Min, Max	7.0, 130.7	(b) (4)	7.0, 140.0	--	--
Change in Number of Weekly Urinary Incontinence Episodes from Baseline at Week 12					
Mean (SD)	-20.0 (27.02)	(b) (4)	-21.9 (25.12)	-19.2 (21.4)	21.0
Median	-16.3	(b) (4)	-18.7	15	19
Min, Max	-105, 86.4	(b) (4)	-95.6, 88.7	--	--
p-value	--	(b) (4)	0.0333	--	0.0265

^aStudy results from Study 1 in the approved labelling for Oxytrol-TDS

. In addition, the efficacy appears to be comparable to the marketed transdermal oxybutynin product, Oxytrol® (Table 2.2.1.1, for detail discussion see Medical Officer's and Statistical Reviews).

Per the discussion with the clinical team and as expected from an anti-cholinergic agent, the most commonly reported adverse events (AEs) was dry mouth. Other observed AEs were constipation and erythema at the application sites. Also, it appears that these AEs were somewhat comparable after 56 mg and 84 mg doses (see Medical Officer's review).

2.2.2 What are the Characteristics of Drug Metabolism?

All oxybutynin available products are available as a racemic (50:50) mixture of R- and S-isomers. Antimuscarinic activity resides predominantly with the R-isomer. Oxybutynin undergoes extensive hepatic metabolism, with less than 0.1% of the administered dose excreted unchanged or metabolite in the urine.

Therefore, due to the high first pass effect, the oral bioavailability of oxybutynin is approximately 6%. The drug is metabolized primarily by CYP3A4 to the main active metabolite N-desethyloxybutynin (DEO) and to the inactive metabolite phenylcyclohexylglycolic acid (PCGA).

2.2.2.1 What is the Rationale for Oxybutynin Gel and Topical Application?

Oral absorption of oxybutynin is rapid, with peak concentrations occurring within 1 h. The elimination half-life of oxybutynin is 1 to 2.3 h. Due to its low oral bioavailability, oxybutynin needs frequent oral dosing, another disadvantage of oral treatment which could be overcome by using the transdermal route of administration

After oral administration, DEO is present in plasma at concentrations much higher than the plasma concentrations of oxybutynin (Figures 2.2.2.1.1 and 2.2.2.1.2). However, as shown in these figures, the ratio between the parent drug, oxybutynin and DEO is reduced after extended release (XL) tablet and topical products.

DEO has anticholinergic effects similar to oxybutynin. However, DEO is believed to be primary responsible for the anticholinergic side effects (mainly dry mouth).

Therefore, delivery by the transdermal route bypasses the substantial hepatic first pass metabolism of oxybutynin. This results in lower circulating concentrations of DEO and hence lower incidence of dry mouth and other unwanted antimuscarinic effects.

Figure 2.2.2.1.1 AUCs of Oxybutynin and DEO Among Oxybutynin Containing Products (Source: Current NDA and Approved Labels)

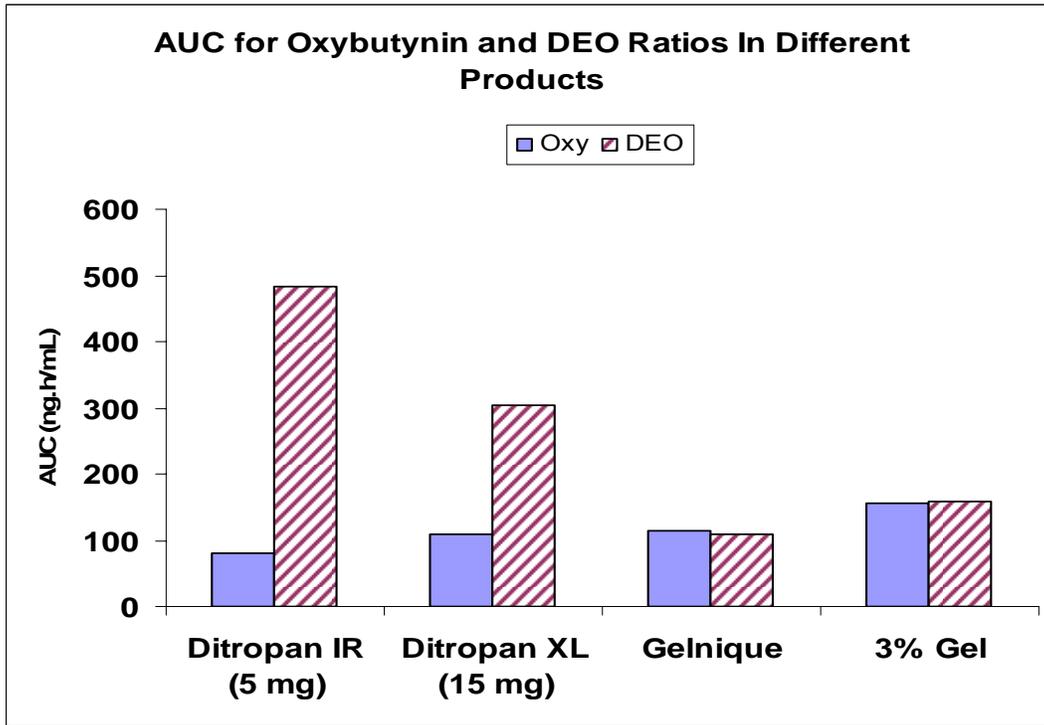
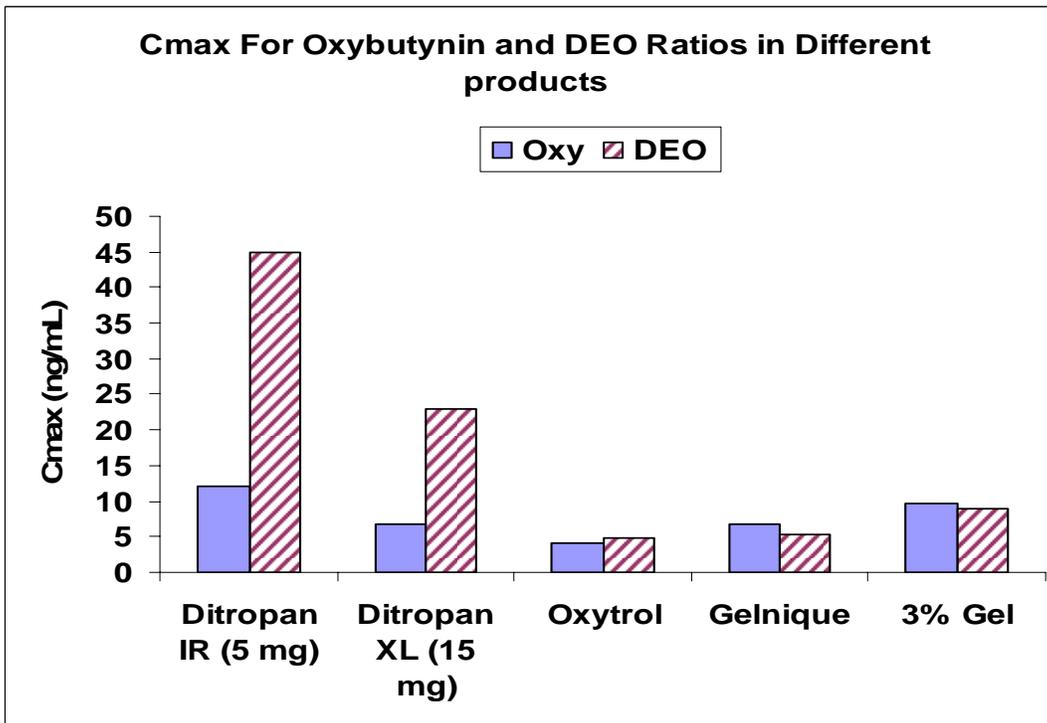


Figure 2.2.2.1.2 Cmax of Oxybutynin and DEO Among Oxybutynin Containing Products (Source: Current NDA and Approved Labels)



2.2.3 Dose-Proportionality

2.2.3.1 What are the characteristics of the 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 as shown in Tables 2.2.3.1 and 2.2.3.2.

Table 1. 2.2.3.1 Treatment Regimens (Study 1034-PhII)

Treatment a:	A single daily dose of 1.4 g of TEST ^a (42 mg oxybutynin), administered each morning for 20 consecutive days
Treatment b:	A single daily dose of 2 g of TEST (60 mg oxybutynin), administered each morning for 20 consecutive days
Treatment c:	A single daily dose of 2.8 g of TEST (84 mg oxybutynin), administered each morning for 20 consecutive days

^a – TEST – oxybutynin gel 3% Batch No. Oxyg146-03B/P1

Table 1. 2.2.3.2 Days of Dosing (Study 1034-PhII)

Table 4: Days of dosing

Treatment Group	Dose	Abdominal Skin Area	Time of Dose	Days
a	42 mg	350cm ²	08:00h	2 through 21
b	60 mg	500 cm ²	08:00h	2 through 21
c	84 mg	700 cm ²	08:00h	2 through 21

The gel was applied to the abdomen in all treatments. The last dose was on day 21 (**Table 2.2.3.2**). 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 oxybutynin and DEO. 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 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 (**Figures 2.2.3.1-2.2.3.3 and Table 2.2.3.3**). However, there was no clear dose proportionality for C_{max} and AUC.

Figure 2.2.3.1. Mean Oxybutynin Plasma Concentration-Time Profiles (Study 1034-PhII)

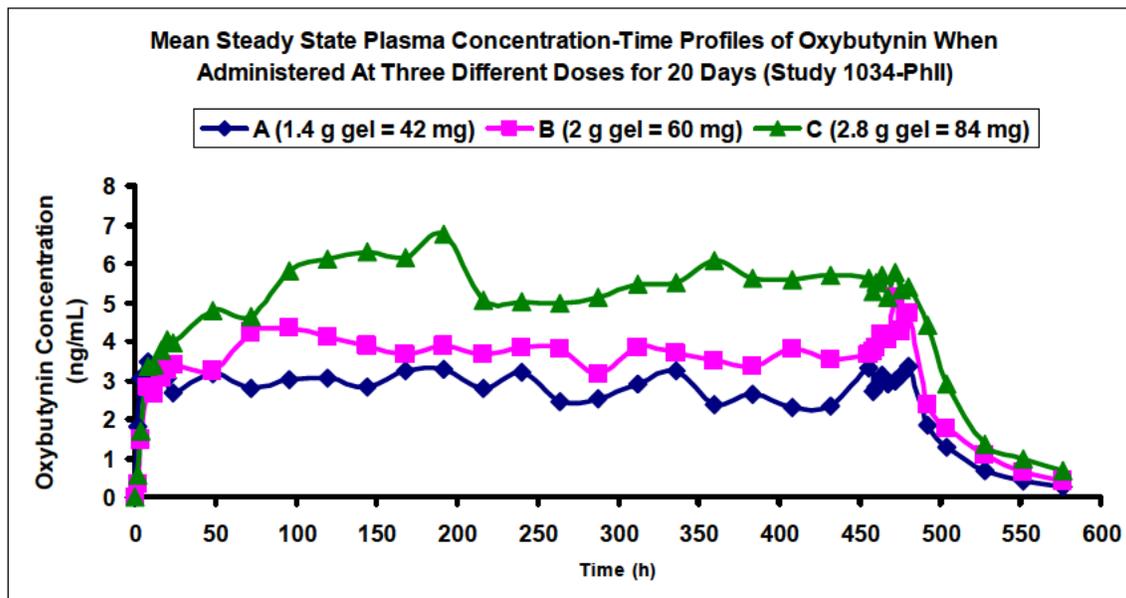


Table 1. 2.2.3.3 Summary of Oxybutynin PK Parameters (Study 1034-PhII)

Dose ^a	Statistic	AUC _{T=0,24} [ng/ml·h]	AUC _{T=5,24} [ng/ml·h]	C _{avg,5d} [ng/ml]	C _{av,55} [ng/ml]	C _{max,5d} [ng/ml]	C _{max,55} [ng/ml]	MR _{5d}	MR ₅₅
1.4 g (45 mg)	N	16	16	16	16	16	16	16	16
	MEAN	70.52	72.51	2.938	3.021	5.193	4.445	1.018	1.007
	SD	103.17	24.27	4.299	1.011	8.417	1.898	0.199	0.307
	Geo_M	46.65	68.95	1.944	2.873	3.279	4.111	0.998	0.961
	Geo_CV	92.0	33.6	92.0	33.579	93.6	41.9	21.486	33.112
2 g (60 mg)	N	16	16	16	16	16	16	16	16
	MEAN	58.95	102.80	2.456	4.283	4.001	6.334	1.105	1.007
	SD	59.59	56.72	2.483	2.363	3.393	3.696	0.289	0.404
	Geo_M	41.76	92.11	1.740	3.838	2.961	5.458	1.072	0.918
	Geo_CV	99.99	49.05	99.989	49.049	95.341	61.107	25.183	50.686
2.8 g (84 mg)	N	16	16	16	16	16	16	16	16
	MEAN	71.88	130.08	2.995	5.420	4.752	7.304	1.070	1.240
	SD	27.32	38.31	1.138	1.596	1.786	2.284	0.230	0.430
	Geo_M	66.94	124.61	2.789	5.192	4.428	6.959	1.047	1.180
	Geo_CV	41.48	31.76	41.483	31.765	41.149	33.727	21.828	32.420

^a dose as g gel (mg oxybutynin). AUC_{T=0,24} – area under the plasma concentration-time curve, single dose; AUC_{T=5,24}: area under the plasma concentration-time curve, steady-state; C_{avg,5d} - average concentration, single dose. C_{av,55} -- average concentration, steady-state; C_{max,5d} - maximum observed plasma concentration, single dose; C_{max,55} - maximum observed plasma concentration, single dose; MR_{5d} – ratio N-desethyloxybutynin/oxybutynin, single dose; MR₅₅ ratio N-desethyloxybutynin/oxybutynin, steady-state

Figure 2.2.3.2. Mean Oxybutynin AUC (0-∞) in All Subjects (Study 1034-PhII)

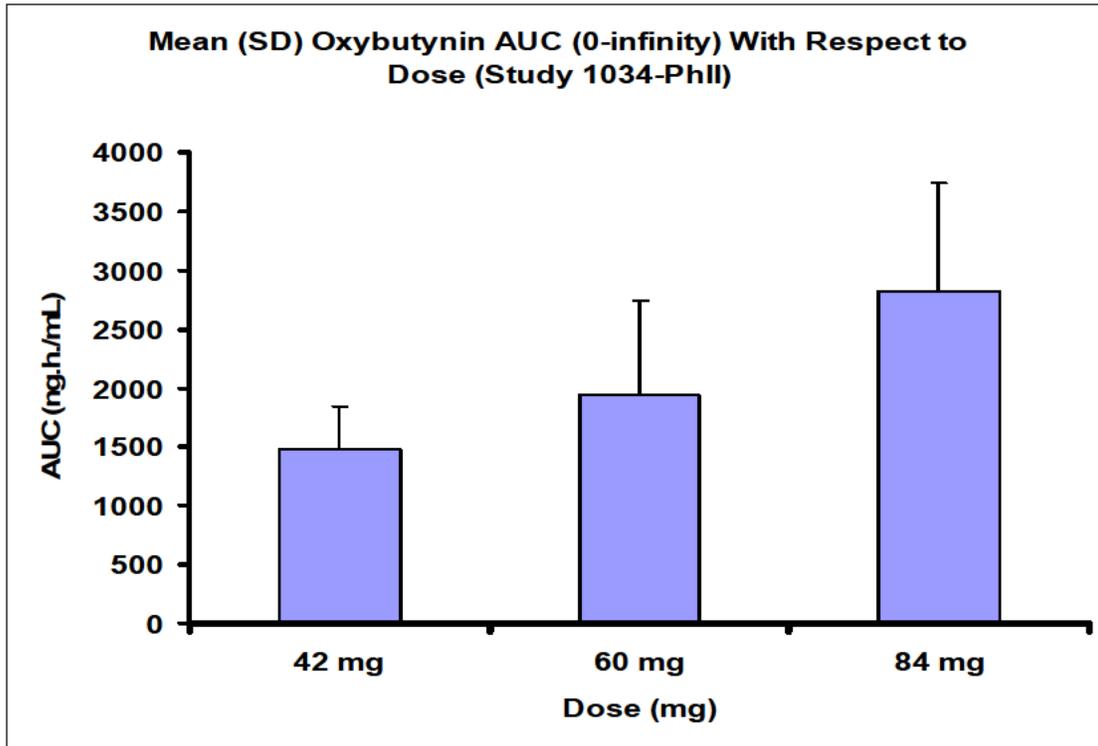
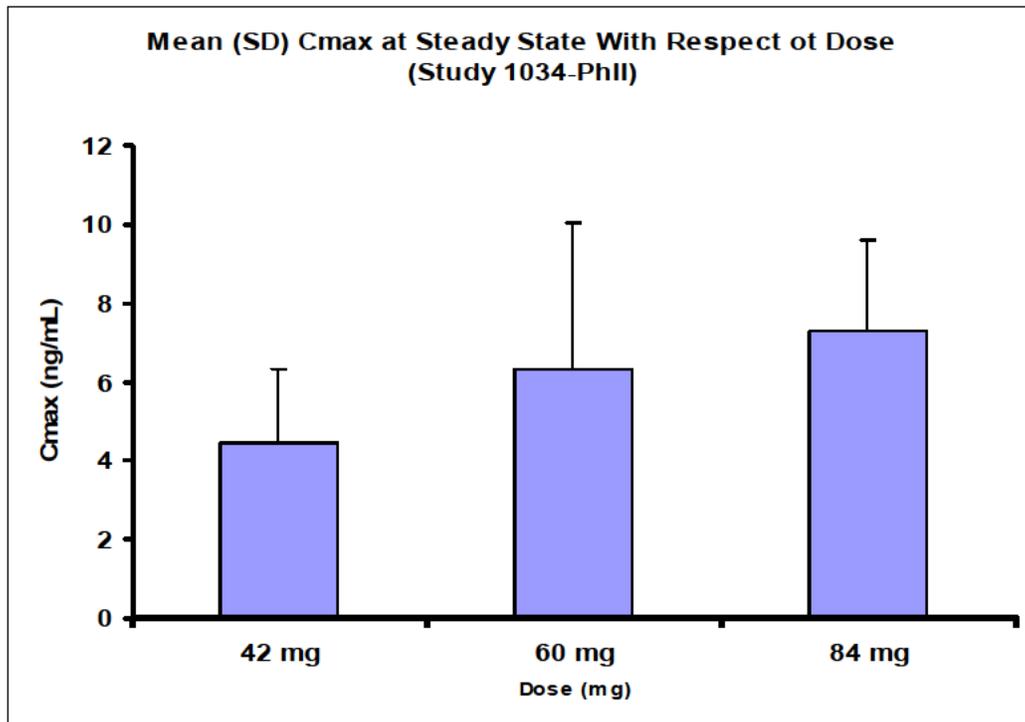


Figure 2.2.3.2. Mean Oxybutynin Cmax and steady State in All Subjects (Study 1034-PhII)



Reviewer's Comments:

It appears that the increase in oxybutynin dose does not necessarily be associated with proportional increase in exposure (i.e., not dose proportional). Thus, the absorption of oxybutynin may be limited by permeability factor rather than the dose. The same conclusion can be made to oxybutynin metabolite, DEO (see Appendix, Section 4.2 for individual study review).

2.2.3.2 Does this Drug Prolong the QT or QTc Interval?

No QTc study was conducted by the sponsor. Oxybutynin has been approved since 1975 as IR tablet under the trade name Ditropan® (NDA 17-577). Since 1970s several formulations containing oxybutynin have been approved. No information is available on the effect oxybutynin on QTc.

2.2.4 What are the PK characteristics of the drug?

2.2.4.1 What are the single and multiple dose PK parameters of oxybutynin and its metabolites? How do the PK parameters change with time following chronic dosing?

No major changes in PK parameters were observed in Phase II multiple dose study for 20 days study (see Study 1034-PhII). There was increase in exposure with dose over 84 mg gel. However, there was no obvious dose proportionality with dose.

2.2.4.2 Is the PK of Oxbutynin dose-proportional?

As stated above, there was no obvious dose proportionality as the dose increased from 42 mg to 84 mg (see Study 1034-PhII).

2.2.4.3 What is the Extent of Systemic Exposure After Oxybutynin Administration?

In addition the Phase II dose-escalation study, the sponsor conducted four studies to establish the systemic exposure of oxybutynin under four conditions:

- Effect of site of application
- Exposure via skin-to skin contact (i.e. partner transfer)
- Effect of sunscreen
- Effect of showering

2.2.4.3.1. Is There Difference in Exposure from Different Application Sites?

The sponsor conducted a study to determine the PK profiles of oxybutynin when applied to three sites (Study #OXYTN/2006/223). This was 3-ways crossover in 25 healthy male and female subjects following 84 mg dose as follows:

Site A: Abdomen (reference site)
Site B: Inner and upper parts of upper thighs (test site)
Site C: Upper arms and shoulders (test site)

Blood samples were collected from each subject over 120 hours following each treatment (site). It appears that the absorption from arms/shoulders is higher than the other two tested sites for both oxybutynin and its metabolite, DEO (Figure 2.4.2.1 and 2.4.2.1 and Table 2.4.2.1). It should be noted that there was wide variability in the data with %CV ranging from approximately 38% to 62% for both C_{max} and AUC following the three sites (Table 2.4.2.1)

Figure 2.4.2.1. Mean Plasma-Concentration-Time Profiles of Oxybutynin When Applied to Three Different Sites (Study #OXYTN/2006/223)

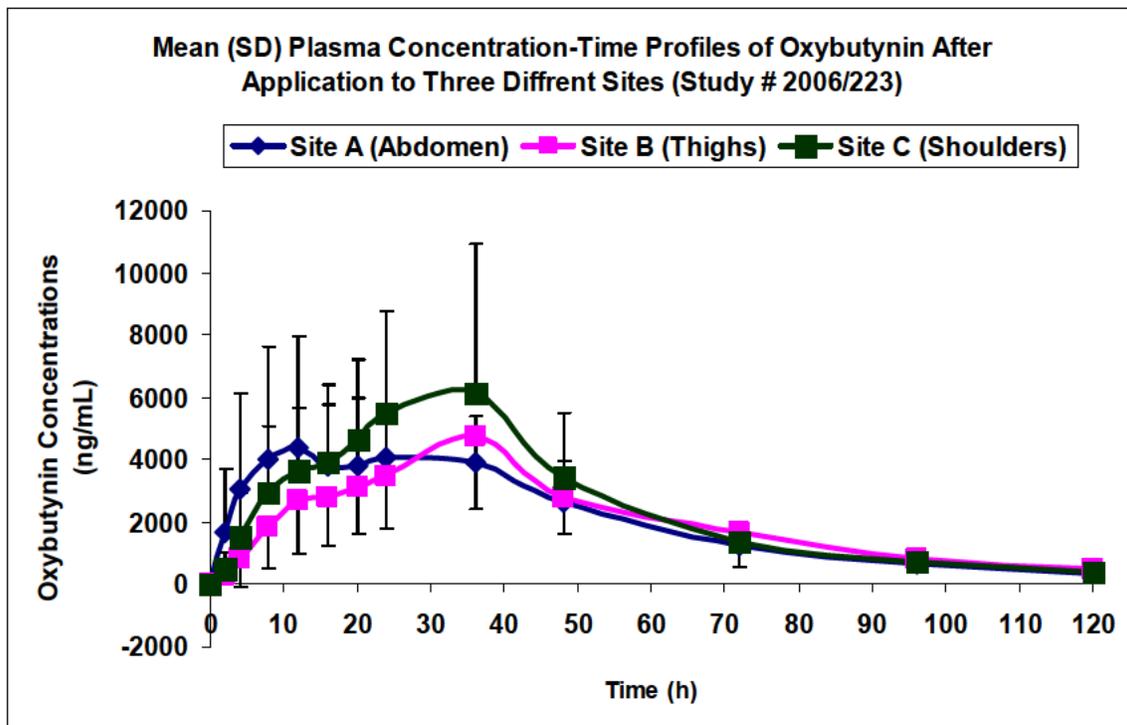


Figure 2.4.2.2. Mean Plasma-Concentration-Time Profiles of DEO When Applied to Three Different Sites (Study #OXYTN/2006/223)

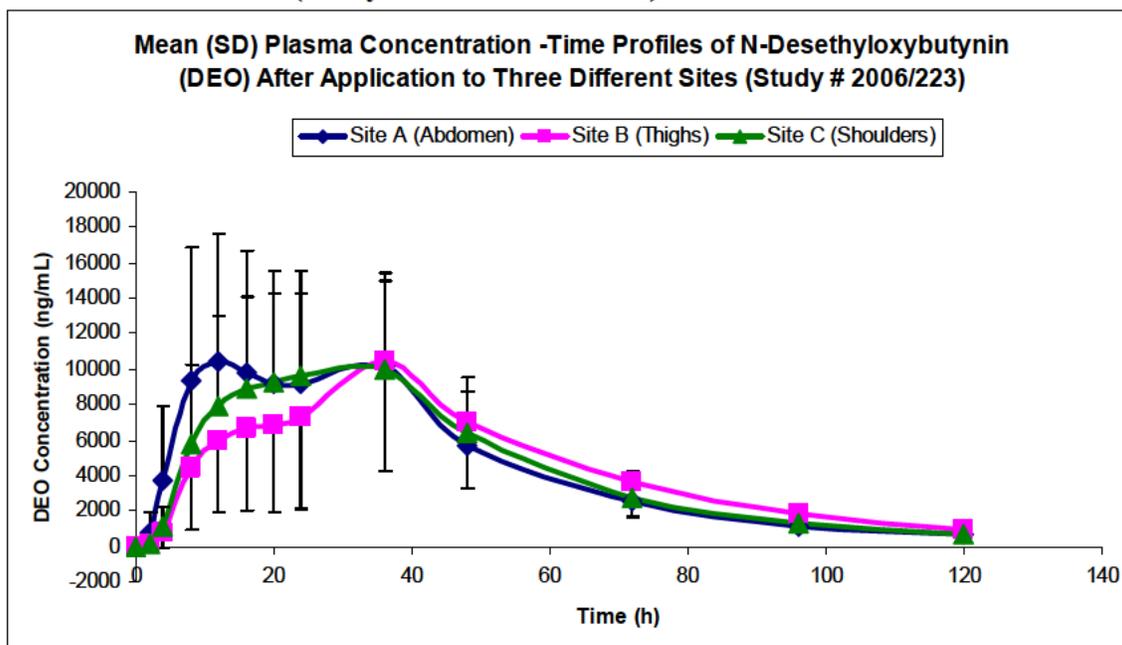


Table 2.4.2.1. Summary of Oxybutynin PK Parameters After Dose Normalization (Study #OXYTN/2006/223)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD		
	Reference Site A (n=25)	Test Site B (n=25)	Test Site C (n=25)
$AUC_{(0-t)}$ (ng·h/mL)	265.758 (38.1) 284.096 \pm 108.17	262.925 (50.6) 286.918 \pm 145.25	302.841 (42.3) 329.051 \pm 139.06
$AUC_{(0-\infty)}$ (ng·h/mL)	280.944 (36.2) 297.776 \pm 107.69	285.036 (48.9) 309.990 \pm 151.68	316.573 (40.7) 342.316 \pm 139.36
C_{max} (ng/mL)	5.628 (55.8) 6.317 \pm 3.53	5.243 (45.1) 5.800 \pm 2.61	7.475 (62.3) 8.811 \pm 5.49
T_{max} (h)	24.00 (4.00 - 48.00)	36.00 (12.00 - 48.00)	24.00 (8.00 - 48.00)

Reviewers Comments:

Considering the variability in the data, it can be concluded that the absorption from the three sites is overall comparable.

2.2.4.3.2. Is There Potential for Transfer of Oxybutynin to Partner Upon Skin-to-Skin Contact?

This question was answered by conducting a partner transfer study following the application of the gel to arms in 14 pairs of healthy partners (Study # SCO 5486). The study was designed as follows:

Treatment A: 84 mg single dose of the gel applied to one arm of one partner. After 2 hours following the application of the gel the partners underwent vigorous arm-to-arm contact for fifteen minutes with the treated arm is **undressed**. The untreated partner had a bare arm.

Treatment B: 84 mg single dose of the gel applied to one arm of one partner. After 2 hours following the application of the gel the partners underwent vigorous arm-to-arm contact for fifteen minutes with the treated arm is **dressed**. The untreated partner had a bare arm.

Blood samples were obtained from the untreated partner at appropriate time intervals over 24 hours. The mean plasma concentration–time profiles of 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 (Figure 2.4.2.2 and Table 2.4.2.2). However, no detectable concentrations of oxybutynin were observed upon contact among all dressed subjects, except one that had one measurable concentration of 0.06 ng/mL (just above the LOQ of the assay of 0.05 ng/mL)

Figure 2.4.2.2. Mean (\pm SD) Plasma-Concentration-Time Profiles of Oxybutynin in Dressed and Undressed Arms (Study #SCO 5486) (Assay LOQ = 0.05 ng/mL)

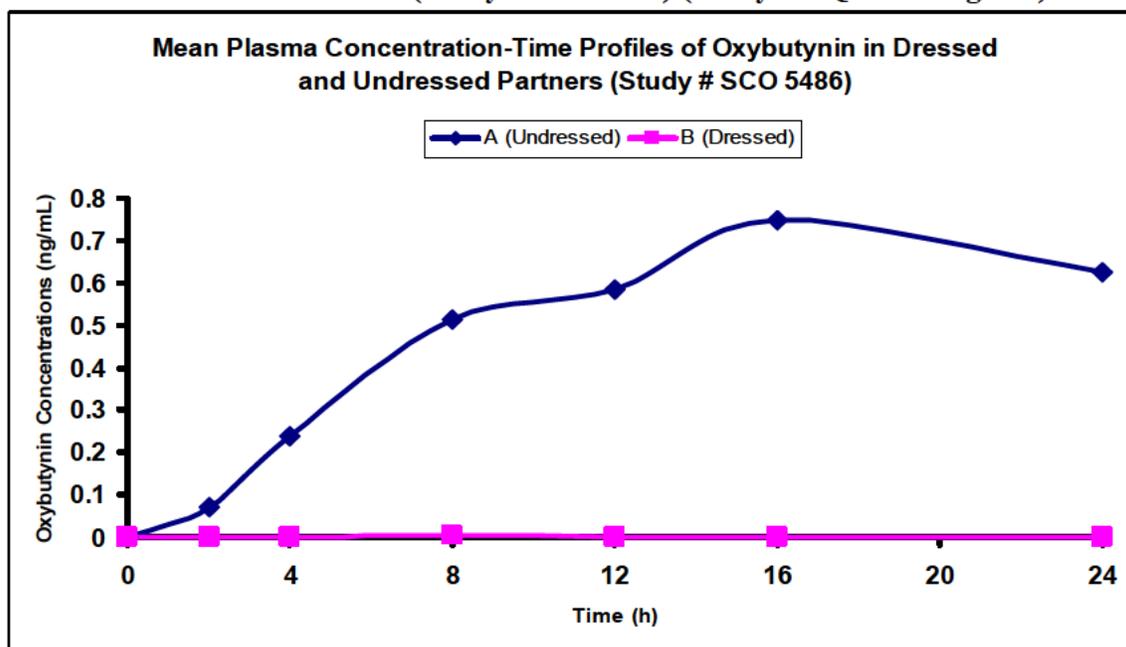


Table 2.4.2.2. Summary of Oxybutynin PK Parameters in Untreated Partners (Study #SCO 5486)

Variable	Statistic	Contact with Undressed Arm	Contact with Dressed Arm
AUC _τ [ng/ml*h]	N	14	14
	Mean	12.220	-
	SD	8.635	-
	GeoM	9.849	.-
	G_CV	77.0	.-
	N x>0	14	1
C _{max} [ng/ml]	N	14	14
	Mean	0.7894	0.0043*
	SD	0.5143	-
	GeoM	0.6555	0.0603**
	G_CV	70.7	-
	N x>0	14	1
t _{max} [h]	N	14	1.
	Mean	18.58	8.00
	SD	4.33	-
	Min	12.00	8.00
	Med	16.02	8.00
	Max	24.02	8.00

GeoM – geometric mean; G_CV – geometric coefficient of variation; N|x>0 – number of subjects with values above the limit of quantitation (LOQ)

*: value based on one concentration > LOQ only (0.0603 ng/ml), the 13 other concentrations were <LOQ.

**: corresponds to the sole value >0/LOQ in subject 010.

2.2.4.3.3. What is the Effect of Sunscreen on the Absorption of Oxybutynin From the Skin?

The sponsor conducted 3-way crossover study in healthy subjects to answer this question (Study # SCO 5487). The study was conducted in 20 healthy subjects as follows:

Treatment A: 84 mg single dose of oxybutynin gel on the abdomen

Treatment B: 84 mg single dose of oxybutynin gel on the abdomen, 30 min before application of sunscreen on the same skin area.

Treatment C: 84 mg single dose of oxybutynin gel on the abdomen, 30 min after application of sunscreen on the same skin area

Blood was collected over 72 hours for the determination of oxybutynin concentration. From this study sunscreen appears to have no effect on the absorption of oxybutynin (**Figure 2.2.4.3 and Table 2.4.2.3**).

Figure 2.4.2.3. Mean Plasma-Concentration-Time Profiles of Oxybutynin With or Without Sunscreen (Study #SCO 5487)

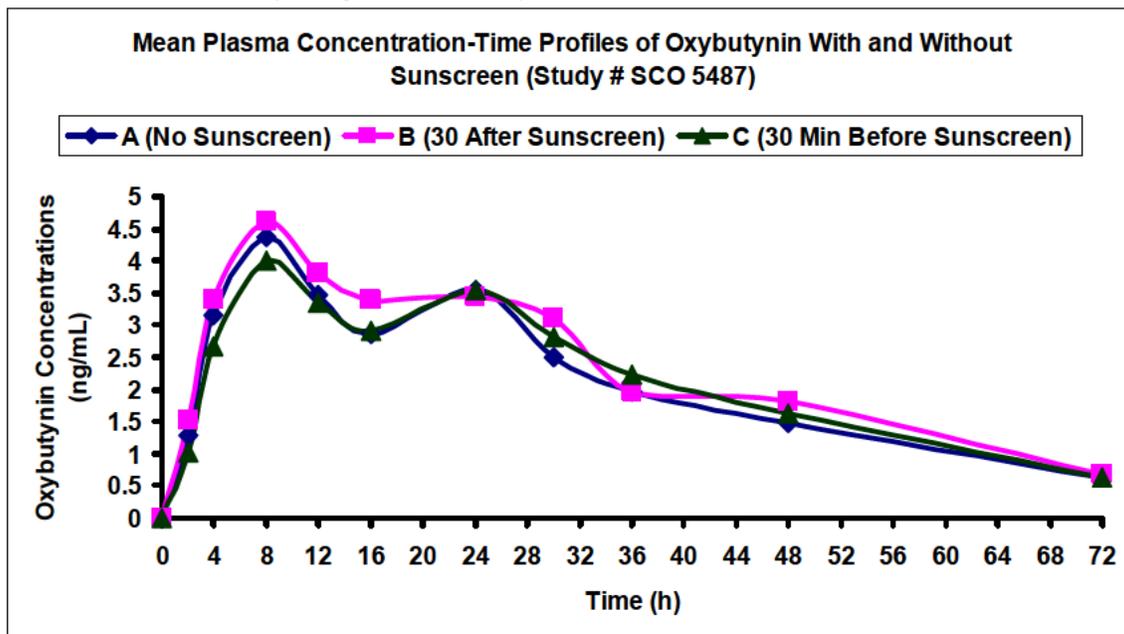


Table 2.4.2.3. Summary of PK Parameters of Oxybutynin With or Without Sunscreen (Study #SCO 5487)

Variable	Statistic	Treatment a	Treatment b	Treatment c
AUC _{0-tz} [ng/ml*h]	N	20	20	20
	Mean	151.380	168.734	154.608
	SD	59.365	87.264	84.263
	GeoM	140.143	147.423	132.010
	G_CV	42.9	59.1	66.2
	N x>0	20	20	20
C _{max} [ng/ml]	N	20	20	20
	Mean	4.9897	5.1798	4.4416
	SD	2.1707	2.8042	2.3472
	GeoM	4.5366	4.3932	3.8172
	G_CV	49.0	68.4	64.9
	N x>0	20	20	20

GeoM – geometric mean; G_CV – geometric coefficient of variation; N|x>0 – number of subjects with values above the limit of quantitation (LOQ)

2.2.4.3.4. Does Showering Affect the Absorption of Oxybutynin From the Skin?

This was a multiple dose study that was designed as a 4-way crossover in 11 healthy couples (i.e., 22 males and females) with no wash between treatment periods (Study # SCO 5488). Prior to the start of first period, subjects received 84 mg dose of the gel on the abdomen for 3 days. Following the three days treatment subjects received the following additional 4 days treatments to ensure steady-state conditions:

Treatment A: 4 further application of 84 mg Oxybutynin on the abdomen and **not showering at all**

Treatment B: 4 further application 84 mg Oxybutynin on the abdomen and showering after **1 hour**

Treatment C: 4 further application 84 mg Oxybutynin on the abdomen and showering after **2 hour**

Treatment D: 4 further application 84 mg Oxybutynin on the abdomen and showering after **6 hours**

Blood samples were collected over 24 hours after the fourth daily dose (i.e., Days 4 and Day 5). Overall, although there was high variability in the data, showering does not appear to affect the absorption of oxybutynin at the tested times in this study (**Figure 2.4.2.4 and Table 2.4.2.4**).

Figure 2.4.2.4. Mean Plasma-Concentration-Time Profiles of Oxybutynin After Showering (Study #SCO 5488)

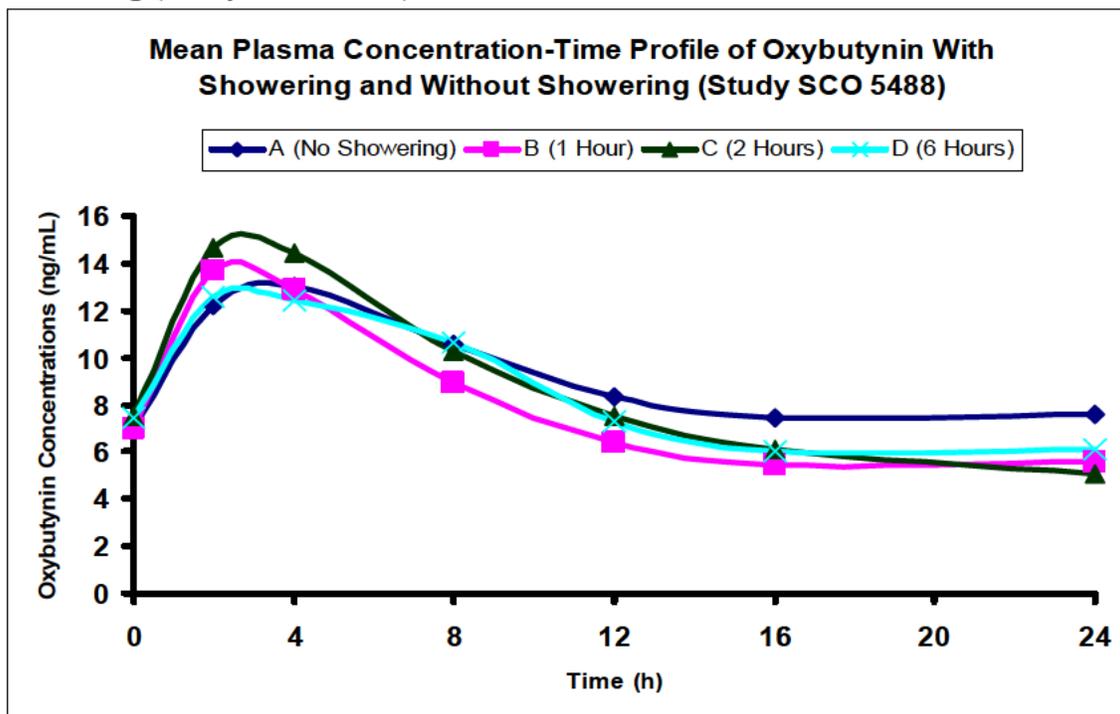


Table 2.4.2.4. Summary of PK Parameters of Oxybutynin After Showering (Study #SCO 5488)

Variable	Statistic	Treatment a	Treatment b	Treatment c	Treatment d
AUC _T [ng/ml*h]	N	22	22	22	22
	Mean	220.285	188.665	207.884	201.745
	SD	111.464	104.007	111.779	90.693
	GeoM	193.208	165.429	183.244	183.438
	G_CV	58.2	55.7	54.4	47.5
	N x>0	22	22	22	22
C _{max} [ng/ml]	N	22	22	22	22
	Mean	14.2875	15.1430	16.9040	15.0636
	SD	8.9758	11.6976	13.0003	9.4368
	GeoM	11.9575	11.9546	13.5876	12.8056
	G_CV	68.1	79.0	73.0	63.5
	N x>0	22	22	22	22

GeoM – geometric mean; G_CV – geometric coefficient of variation; N|x>0 – number of subjects with values above the limit of quantitation (LOQ). Treatments: a – no showering; b: showering 1 hr after application of Anturool; c: showering 2 hr after application; d: showering 6 hr after application.

Reviewer’s Comments:

Based on this data, it is recommended that showering should be withheld until 1 hour has passed after the application of the gel. This statement or similar language should be included in the label.

2.3 Intrinsic factors

2.3.1 Does age, weight, race, or disease state affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

No formal demographic or special population studies were conducted with oxybutynin 3% gel to investigate the effect of age, weight, race, renal or hepatic impairment or disease state on the PK and/or PD of the drug.

2.4 Extrinsic factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

No formal studies to establish the effect of drug-drug interaction or the effect of externally ingested drugs or herbs were conducted by the sponsor with 3% gel. However, the sponsor conducted two studies to investigate the effect of sunscreen and showering (as extrinsic factor) on the absorption of oxybutynin from the gel. These studies are

previously discussed. From these studies it was concluded that neither sunscreen nor showering had any major effect on oxybutynin systemic exposure.

2.5 General Biopharmaceutics

2.5.1 What is the Biopharmaceutics Classification System (BCS) Class Classification for Oxybutynin?

The sponsor did not provide information about the BCS classification of oxybutynin. This information is not applicable for this submission.

2.5.2.1 What is the Absolute Bioavailability of Oxybutynin?

The sponsor did not provide information on the absolute bioavailability of 3% gel. However, according the most recently revised oxybutynin IR tablet (Ditropan®) label dated August 8, 2011 the absolute bioavailability of oxybutynin tablet is about 6% (ranging from 1.6% to 10.9%).

As indicated earlier, oxybutynin is rapidly absorbed achieving C_{max} within an hour after oral administration. The effective half-life is approximately 2 to 3 hours. Wide inter-individual variation in PK parameters was observed following oral administration of oxybutynin.

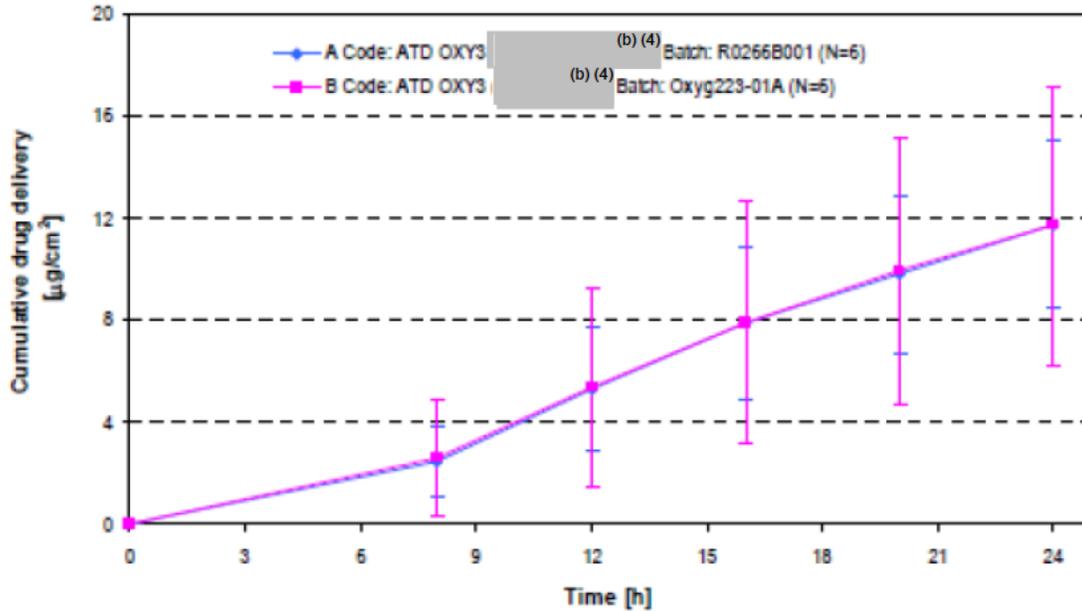
2.5.3 Was the to-be-Marketed (TBM) Formulation Used in the Clinical Trials?

Background and Rationale:

As stated earlier, the formulation of oxybutynin 3% gel used in initial clinical trials was found to (b) (4) (b) (4) suspected to be potential carcinogenic and genotoxic in animal studies. (b) (4)

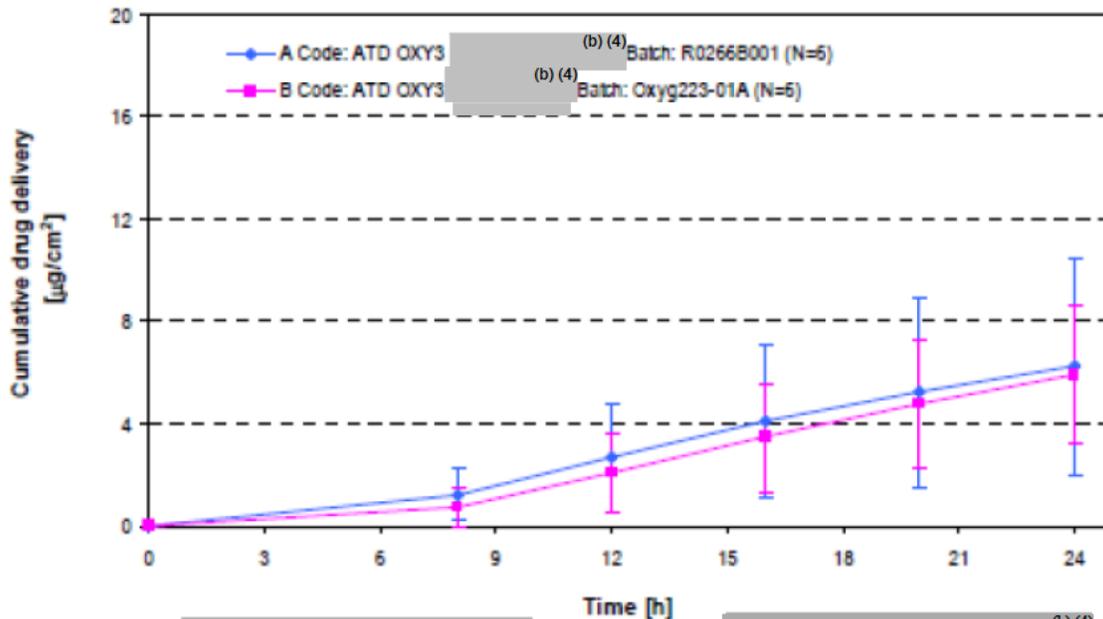
(b) (4) Therefore, the Sponsor evaluated the effect of this change in *ex vivo* skin penetration studies using both pig and human skin (Study AP-1034). The results of this study indicated that the formulation change had no significant effect on skin penetration (**Figures 2.5.3.1 and 2.5.3.2, see also CMC reviews for details**).

Figure 2.5.3.1 Ex Vivo Transdermal Oxybutynin Cumulative Delivery from 3% Gel Formulations in Pig Skin



Formulation A: (b) (4) Formulation B: (b) (4)

Figure 2.5.3.2 Ex Vivo Transdermal Oxybutynin Cumulative Delivery from 3% Gel Formulations in Human Skin



Formulation A: (b) (4) Formulation B: (b) (4)

Based on the *ex Vivo* data, a comparative bioavailability study comparing the old (Reference) and new (Test) formulations was conducted (see below).

This changes in formulations occurred during Phase III trial after 130 patients were studied using (b) (4) (old formulation). The Phase III study was completed with the new formulation (b) (4). The composition of the formulation (b) (4) was shown earlier in Table 2.1.1.3. Several other studies were conducted using formulation (b) (4) as shown in Table 2.5.3.1.

Table 2.5.3.1. Summary of Gel Formulations Used in Clinical Studies

Study No. Study Report Location	Formulation Number (b) (4)	Oxybutynin Content (%)	Batch Number(s)	Description of Change	Reason for change
OXPk2 (5.3.1.1-1)	(b) (4)	3	031101	NA	NA
1034-PhII (5.3.1.2-1)		3	Oxyg146-03B/P1	New Batch	NA
OXBTN/2006/223 (5.3.1.2)		3	C0900A001	New Batch	NA
SCO 5432 (5.3.1.2-2)		3	Oxyg 146-20B/P1 (b) (4) Oxyg 223-05B/P1 (b) (4)	New formulation (b) (4) for comparison with older formulation (b) (4)	Changed original formulation (b) (4) (b) (4)
SCO 5486 (5.3.1.1-4)		3	HKB	New Batch	NA
SCO 5487 (5.3.1.1-5)		3	HKB	NA	NA
SCO 5488 (5.3.1.1-3)		3	HKB	NA	NA
20070060 (5.3.5.1)		3	C0847B001	Initial Batch for Phase 3 Study (Anturol)	NA
		3	R0266B003	Batch for Phase 3 Study (b) (4)	
		3	HKB	Backup Batch for Phase 3 Study (b) (4)	
20070060 (5.3.5.1)		Placebo	C0846B001	Batch for Phase 3 Study (Placebo)	NA
		Placebo	R0267B002	Batch for Phase 3 Study (b) (4)	(b) (4)

Are the Two Formulation Equivalent?

Due to the change in formulation a bioequivalence study was required to establish the link between the old formulation (b) (4) and the new formulation (Table 2.5.3.2).

Table 2.5.3.2. Formulations (b) (4) for Bioequivalence (Study SCO 5432)

Drug 2: Formulation (b) (4) (b) (4) TEST (treatment a) Dose: 2.8 g qd (84 mg oxybutynin)	name: substance: strength: dosage form: mode/route: batch no.: Company Responsible for manufacturing the product	Test Oxybutynin 3% gel transdermal oxyg 223-05B/P1 Antares Pharma, Inc
Drug 1: Formulation (b) (4) REFERENCE (treatment b) Dose: 2.8 g qd (84 mg oxybutynin)	name: substance: strength: dosage form: mode/route: batch no.: Company Responsible for manufacturing the product	Reference Oxybutynin 3% gel transdermal oxyg 146-20B/P1 Antares Pharma, Inc

Study Design:

The study was designed as multiple-dose (7 days), randomized, 2-period cross-over with 14 days washout period in 58 healthy subjects (32 females and 26 males) at a dose of 84 mg applied to abdomen.

All subjects applied a single daily dose of 2.8 gram of gel (each containing 84 mg oxybutynin) to a skin area of 700 cm² on the abdomen for 7 days. Blood samples were collected at baseline on Days 1 and on Days 7 over 264 hours as follows:

Day 1: 00:00 (immediately before application)

Day 7: 144:00; 146:00; 148:00; 152:00; 156:00

Day 8: 160:00; 164:00; 168:00; day 9: 192:00

Day 12: 264:00 hours after the first administration of the study medication

From this study, the exposure for both the parent drug, oxybutynin, and its metabolite, DEO, following the new formulation (b) (4) (treatment A, test is higher than that of the old formulation (b) (4) (treatment B, reference) as shown in **Figures 2.5.3.3 and 2.5.3.4 and Tables .**

Figure 2.5.3.3. Mean Plasma Concentration-Time Profiles for Oxybutynin: Treatment A: New Formulation (b) (4) and treatment B: Old (reference) formulation (b) (4) (Study SCO 5432)

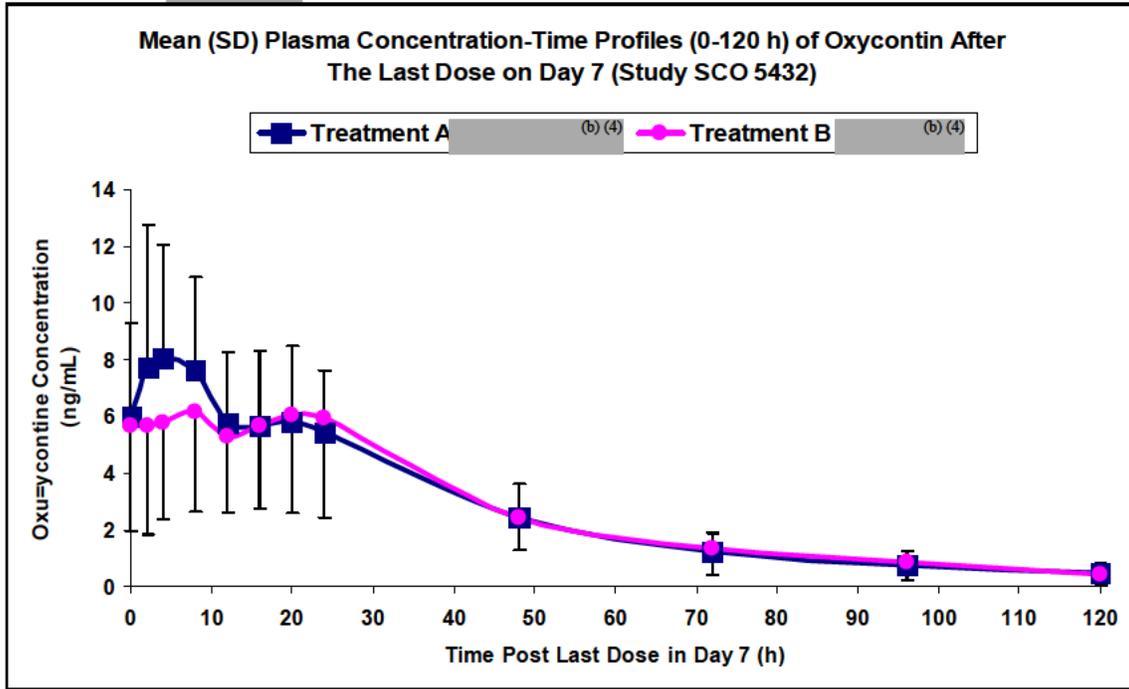


Figure 2.5.3.4. Mean Plasma Concentration-Time Profiles for DEO: Treatment A: New Formulation (b) (4) and treatment B: Old (reference) formulation (b) (4) (Study SCO 5432)

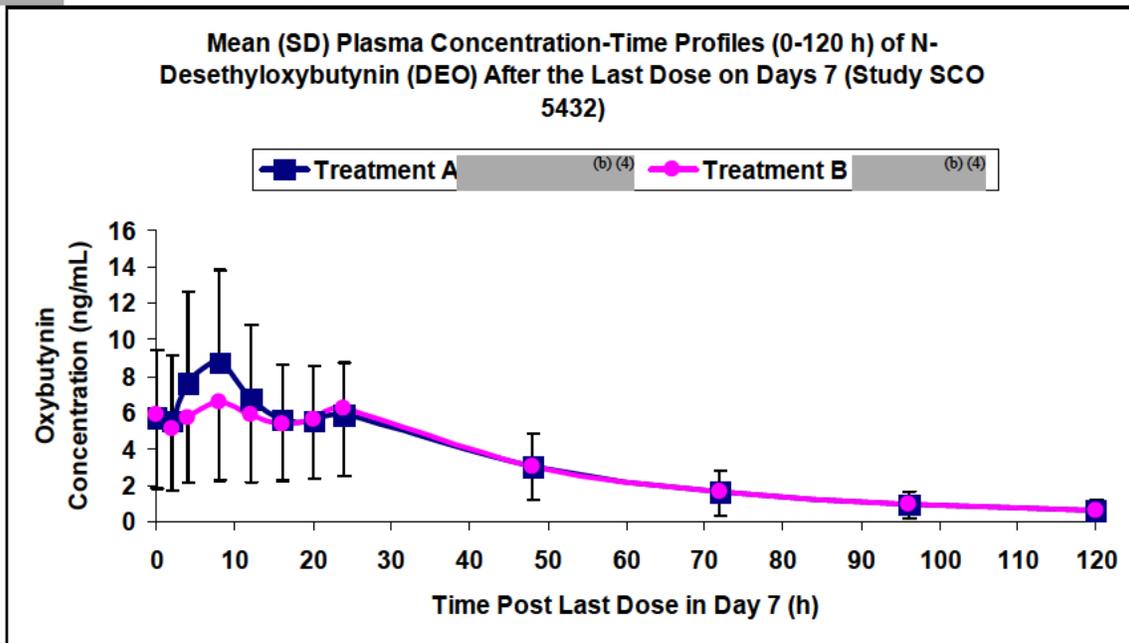


Table 2.5.3.2. Summary of PK Parameters for Oxybutynin: Treatment A: New Formulation (b)(4) and treatment B: Old (reference) formulation (b)(4) (Study SCO 5432)

Variable	Stat.	a	b
AUC_T [ng/ml*h]	N	54	54
	Mean	156.0676	139.0606
	SD	62.7989	70.7830
	GeoM	143.6709	124.1565
	G_CV	44.4	50.4
C_{av} [ng/ml]	N	54	54
	Mean	6.5028	5.7942
	SD	2.6166	2.9493
	GeoM	5.9863	5.1732
	G_CV	44.4	50.4
C_{max} [ng/ml]	N	54	54
	Mean	9.7444	8.0979
	SD	5.1062	4.9407
	GeoM	8.6067	6.9707
	G_CV	54.7	58.2
C_{min} [ng/ml]	N	54	54
	Mean	4.3767	4.2269
	SD	1.8940	2.0866
	GeoM	4.0096	3.7715
	G_CV	44.5	51.6
PTF	N	54	54
	Mean	0.77	0.62
	SD	0.31	0.33
	GeoM	0.71	0.55
	G_CV	41.7	55.5
R (coefficient of correla- tion)	N	54	54
	Min	-1.000	-1.000
	Med	-0.994	-0.994
	Max	-0.863	-0.891
t_{1/2} [h]	N	54	54
	Mean	29.18	29.92
	SD	8.35	9.61
	GeoM	28.16	28.65
	G_CV	26.7	29.4
t_{max} [h]	N	54	54
	Mean	6.67	10.11
	SD	6.20	8.37
	CV	93.0	82.8
	Min	0.00	0.00
	Med	4.00	8.00
	Max	24.00	24.00
T_{cav} [h]	N	54	54
	Mean	10.42	10.52
	SD	1.69	2.14
	CV	16.2	20.3
	Min	7.24	5.32
	Med	10.27	10.41
	Max	15.05	16.34

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day (84 mg oxybutynin/day)

Table 2.5.3.3. Summary of PK Parameters for DEO: Treatment A: New Formulation (b)(4) and treatment B: Old (reference) formulation (b)(4) (Study SCO 5432)

Variable	Stat.	a	b
AUC_T [ng/ml*h]	N	54	54
	Mean	157.7218	139.4513
	SD	88.6001	84.0210
	GeoM	137.7699	119.5782
	G_CV	55.3	59.5
C_{av} [ng/ml]	N	54	54
	Mean	6.5717	5.8105
	SD	3.6917	3.5009
	GeoM	5.7404	4.9824
	G_CV	55.3	59.5
C_{max} [ng/ml]	N	54	54
	Mean	8.9495	7.2829
	SD	5.3402	4.2883
	GeoM	7.6858	6.2690
	G_CV	59.2	58.9
C_{min} [ng/ml]	N	54	54
	Mean	4.6255	4.4706
	SD	2.6520	2.8876
	GeoM	4.0281	3.7590
	G_CV	56.0	63.8
PTF	N	54	54
	Mean	0.64	0.50
	SD	0.23	0.21
	GeoM	0.59	0.46
	G_CV	40.3	44.0
R (coefficient of correlation)	N	54	54
	Min	-1.000	-1.000
	Med	-0.996	-0.996
	Max	-0.872	-0.882
t_½ [h]	N	54	54
	Mean	31.17	31.42
	SD	8.42	12.62
	GeoM	30.11	29.88
	G_CV	27.0	30.1
t_{max} [h]	N	54	54
	Mean	7.97	11.78
	SD	4.44	9.33
	Min	0.00	0.00
	Med	8.00	8.00
	Max	24.00	24.00
T_{Cav} [h]	N	54	54
	Mean	10.79	11.65
	SD	1.55	2.13
	Min	6.96	6.82
	Med	10.63	11.44
	Max	13.61	17.37

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

In addition, the 90% CI for both the parent and the metabolites are not within 80% to 125% bioequivalence limits (**Tables 2.3.3.4 and 2.3.3.5**).

Table 2.5.3.4. Oxybutynin 90% Confidence Intervals (CI) (Study SCO 5432)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{av}	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 _{1/2}	ANOVA	log	a/b	98.33	91.76	105.37	21.7
T _{Cav}	ANOVA	lin	a-b	-0.09	-0.73	0.54	18.8
t _{max}	HAUSCHKE	lin	a-b	-4.00	-6.00	-1.00	

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

Table 2.5.3.4. DEO 90% Confidence Intervals (CI) (Study SCO 5432)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{av}	ANOVA	log	a/b	115.43	106.10	125.58	26.6
C _{max}	ANOVA	log	a/b	122.90	112.63	134.10	27.5
C _{min}	ANOVA	log	a/b	107.22	97.40	118.03	30.5
PTF	ANOVA	log	a/b	130.36	116.11	146.36	37.1
t _{1/2}	ANOVA	log	a/b	101.20	94.73	108.11	20.7
T _{Cav}	ANOVA	lin	a-b	-0.86	-1.43	-0.29	15.1
t _{max}	HAUSCHKE	lin	a-b	-4.00	-6.02	-0.01	

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

Reviewer's Comments:

Based on this study, it can be concluded that the two formulations are **not** bioequivalent. Since the exposure after the new formulation (b)(4) (Treatment A) is higher than that of the old formulation (b)(4) (treatment B) and the drug is historically relatively safe and at the proposed dose of 84 mg, the inclusion of the 130 patients from the Phase III study who have been treated with the old formulation is acceptable from the clinical pharmacology perspective. The reason for the inclusion of the 130 patients in the analysis of the data is to improve the statistical power of the trial to establish the efficacy of the treatment with the new oxybutynin gel.

However, it should be emphasized that from the clinical pharmacology perspective **the two formulations are not demonstrated to be bioequivalent.**

2.5.4 What are the Biopharmaceutical Characteristics of the Products?

This is a metered-dose pump containing 3% oxybutynin gel. The pump delivers per actuation 0.92 gram of gel (1.0 ml) that is equivalent to 28 mg oxybutynin. The composition of the formulation has been discussed in earlier sections and in particular Section 2.1.1.

2.6 Analytical Section

The concentration of oxybutynin and DEO was determined in the plasma samples using a validated LC-MS/MS method. The assay exhibits linearity over a concentration range of 75 pg/mL to 7000 pg/mL (0.075 to 70 ng/ml) for both oxybutynin and DEO in human plasma.

The LLOQ of the assay for both the parent and the metabolite is 0.05 ng/ml (50 pg/mL). Accuracy and precision data for both compounds are shown in **Tables 2.6.1 to 2.6.4**.

From these data, it can be concluded that the method is sensitive, accurate and reproducible.

Table 2.6.1 Intra Assay Accuracy and Precision for Oxybutynin

Run 1	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.04331	0.13041	20.11624	39.61254
SD (ng/ml)	0.00662	0.01495	0.36811	1.01971
CV (%)	15.3	11.5	1.8	2.6
Accuracy (%)	86.6	93.1	100.6	99.0
N	6	6	6	6
Run 2	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.04644	0.14961	20.18423	38.68444
SD (ng/ml)	0.00503	0.01327	0.29551	0.39941
CV (%)	10.8	8.9	1.5	1.0
Accuracy (%)	92.9	106.9	100.9	96.7
N	6	6	6	6
Run 3	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.04201	0.13258	20.51633	40.27134
SD (ng/ml)	0.00454	0.00428	0.34259	1.08535
CV (%)	10.8	3.2	1.7	2.7
Accuracy (%)	84.0	94.7	102.6	100.7
N	6	6	6	6

Table 2.6.2 Inter Assay Accuracy and Precision for Oxybutynin

	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Global Mean (ng/ml)	0.04392	0.13753	20.27227	39.52277
SD (ng/ml)	0.00548	0.01417	0.36389	1.07139
CV (%)	12.5	10.3	1.8	2.7
Accuracy (%)	87.8	98.2	101.4	98.8

Table 2.6.3 Intra Assay Accuracy and Precision for DEO

Run 1	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.05594	0.13139	20.72970	40.30638
SD (ng/ml)	0.01119	0.01666	0.52700	3.67536
CV (%)	20.0	12.7	2.5	9.1
Accuracy (%)	111.9	93.9	103.6	100.8
N	6	6	6	6
Run 2	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.05213	0.14861	20.46928	40.12857
SD (ng/ml)	0.00577	0.00686	0.94922	1.70468
CV (%)	11.1	4.6	4.6	4.2
Accuracy (%)	104.3	106.2	102.3	100.3
N	6	6	6	6
Run 3	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Mean (ng/ml)	0.04625	0.15035	21.37129	40.57274
SD (ng/ml)	0.00622	0.00623	0.59903	1.76341
CV (%)	13.4	4.1	2.8	4.3
Accuracy (%)	92.5	107.4	106.9	101.4
N	6	6	6	6

Table 2.6.4 Inter Assay Accuracy and Precision for DEO

	LLOQ (0.05 ng/ml)	QCA (0.14 ng/ml)	QCB (20 ng/ml)	QCC (40 ng/ml)
Global Mean (ng/ml)	0.05144	0.14345	20.85676	40.33590
SD (ng/ml)	0.00865	0.01358	0.77740	2.40366
CV (%)	16.8	9.5	3.7	6.0
Accuracy (%)	102.9	102.5	104.3	100.8

3.0 Labeling Comments: There are no major labeling comments from the clinical pharmacology perspective that are vastly different from that in the currently approved labels for oxybutynin. However, the main clinical pharmacology comments will be related to the results from the effect of showering, sunscreen, partner transfer, and site of application studies. The conclusions from these studies are already proposed by the sponsor in the draft label. Therefore, some editorial work will be made directly into the draft label before and during the labeling discussions.

16 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

4.2 Selected Individual Study Review:

This section contains detailed reviews of selected studies that are most relevant from the clinical pharmacology perspective.

4.2.1 Study # SCO 5432 (Bioequivalence Study)

Study Title: Single-center, multiple-dose, open-label, randomized, 2-period crossover bioequivalence study on two 3 % gel formulations of oxybutynin at a dosage of 84 mg daily in healthy subjects

Rationale:

As stated in several sections of this review that the formulation of oxybutynin 3% gel used in initial clinical trials was found to contain traces of (b) (4). This impurity (b) (4) is suspected to be carcinogenic and genotoxic in animal studies. Therefore, the sponsor changed the formulation (b) (4).

(b) (4). Therefore, the main rationale for this study is to establish the link between the old formulation (b) (4) and the new formulation (b) (4) (Table 4.2.1.1).

Table 4.2.1.1 Formulations (b) (4) for Bioequivalence (Study SCO 5432)

Drug 2: Formulation (b) (4) TEST (treatment a) Dose: 2.8 g qd (84 mg oxybutynin)	name: substance: strength: dosage form: mode/route: batch no.: Company Responsible for manufacturing the product	Test Oxybutynin 3% gel transdermal oxyg 223-05B/P1 Antares Pharma, Inc
Drug 1: Formulation (b) (4) REFERENCE (treatment b) Dose: 2.8 g qd (84 mg oxybutynin)	name: substance: strength: dosage form: mode/route: batch no.: Company Responsible for manufacturing the product	Reference Oxybutynin 3% gel transdermal oxyg 146-20B/P1 Antares Pharma, Inc

Objectives: To assess the bioequivalence of oxybutynin from Reference (b) (4) and from Test formulation (b) (4).

Design:

The study was designed as multiple-dose (7 days), randomized, 2-period cross-over with 14 days washout period in 58 healthy subjects (32 females and 26 males) ages from 18 to 55 years at a dose of 84 mg applied to abdomen. All subjects applied a single daily dose of 2.8 gram of 3% gel (each containing 84 mg oxybutynin) to a skin area of 700 cm² on the abdomen as follows:

Treatment A (Test): multiple doses of 2.8 g of 3% Oxybutynin gel (84 mg oxybutynin) per day, administered each morning for 7 consecutive days ((Batch # oxyg 223-05B/P1)

Treatment B (Reference): multiple doses of 2.8 g of 3% Oxybutynin gel (84 mg oxybutynin) per day, administered each morning for 7 consecutive days ((Batch # oxyg 146-20B/P1)

All subjected fasted over night (for at least 12 hours) the night before the last dose on day 7 and until 2 hours after the application of the gel on day 7. Blood samples were collected at baseline on Days 1 and on Days 7 over 264 hours as follows:

Day 1: 00:00 (immediately before application)

Day 7: 144:00; 146:00; 148:00; 152:00; 156:00

Day 8: 160:00; 164:00; 168:00;

Day 9: 192:00

Day 11: 240

Day 12: 264:00 hours after the first administration of the study medication

Blood was drawn directly from a vein into EDTA-coated tubes and kept in an ice bath for a maximum of 30 min until centrifugation.

The concentration of oxybutynin and N-desethyloxybutynin (DEO) was determined in the samples using an LC-MS/MS method. One aliquot of 1 ml was analyzed from each sample. The calibration range is set to 0.05 –50 ng/ml for oxybutynin and for DEO.

Results:

From this study it, the exposure for both the parent drug, oxybutynin, and its metabolite, N-Desethyloxybutynin (DEO), following the new formulation (b) (4) (Treatment A, test) is higher than that of the old formulation (b) (4) (Treatment B, reference) as shown in **Figures 4.2.1.1 and 4.2.1.2 and Tables 4.2.1.2 and 4.2.1.3).**

Figure 4.2.1.1 Mean Plasma Concentration-Time Profiles for Oxybutynin: Treatment A: New Formulation (b) (4) and treatment B: Old (reference) formulation (b) (4) (Study SCO 5432)

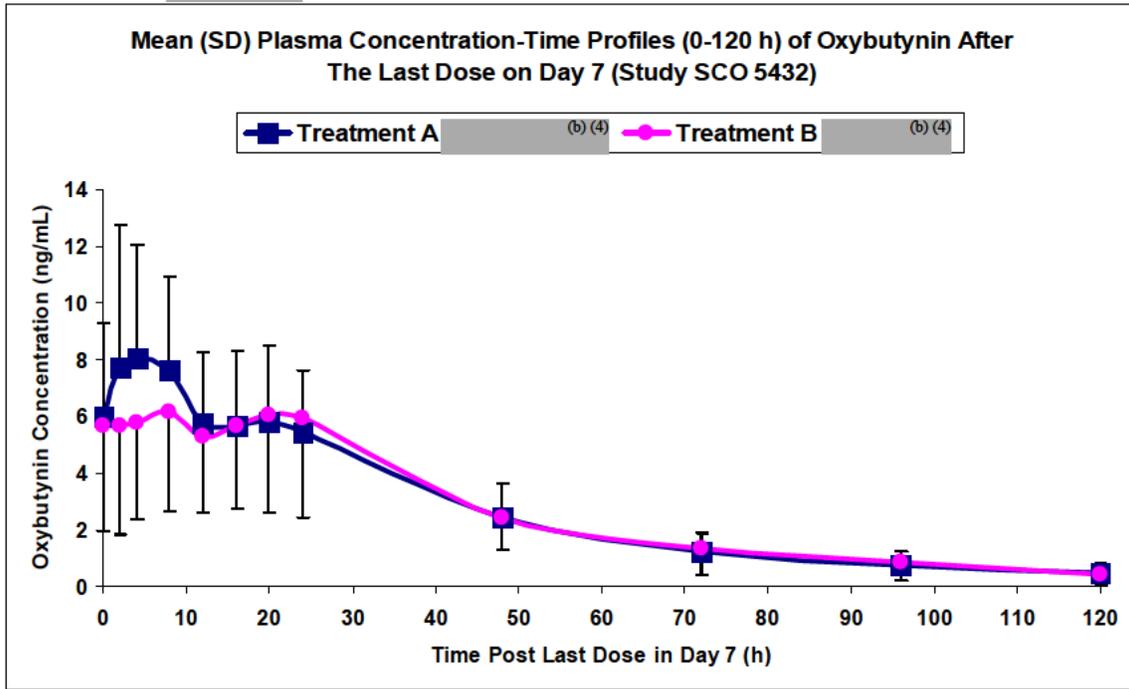


Figure 4.2.1.2. Mean Plasma Concentration-Time Profiles for N-Desethyloxybutynin: Treatment A: New Formulation (b) (4) and treatment B: Old (reference) formulation (b) (4) (Study SCO 5432)

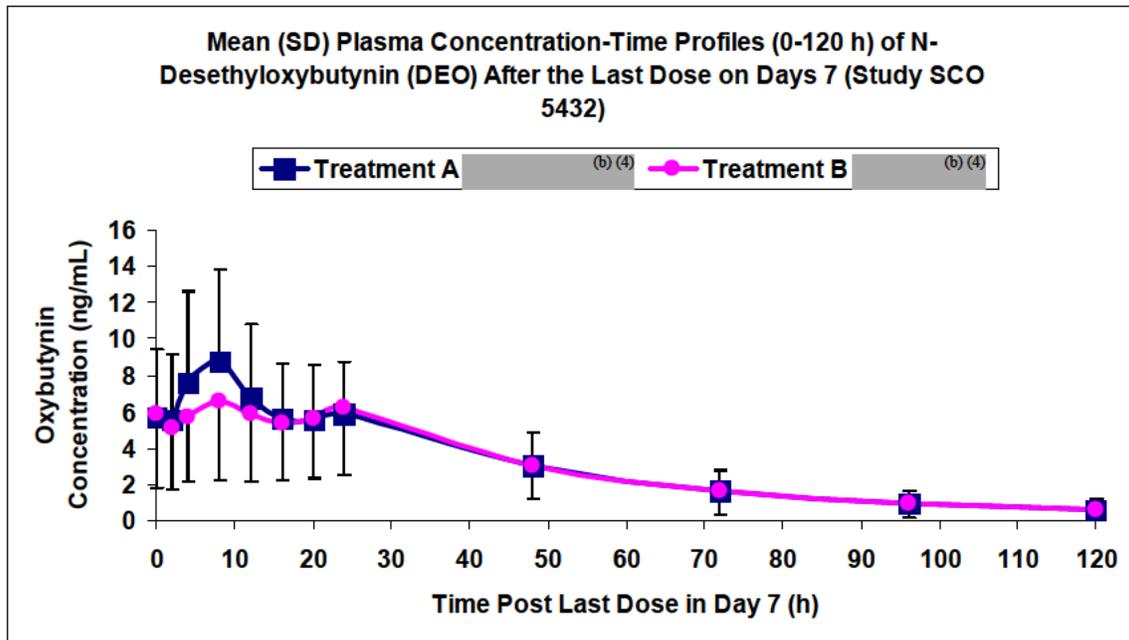


Table 4.2.1.2 Summary of PK Parameters for Oxybutynin: Treatment A: New Formulation (b) (4) and treatment B: Old (reference) formulation (b) (4) (Study SCO 5432)

Variable	Stat.	a	b
AUC_T [ng/ml*h]	N	54	54
	Mean	156.0676	139.0606
	SD	62.7989	70.7830
	GeoM	143.6709	124.1565
	G_CV	44.4	50.4
C_{av} [ng/ml]	N	54	54
	Mean	6.5028	5.7942
	SD	2.6166	2.9493
	GeoM	5.9863	5.1732
	G_CV	44.4	50.4
C_{max} [ng/ml]	N	54	54
	Mean	9.7444	8.0979
	SD	5.1062	4.9407
	GeoM	8.6067	6.9707
	G_CV	54.7	58.2
C_{min} [ng/ml]	N	54	54
	Mean	4.3767	4.2269
	SD	1.8940	2.0866
	GeoM	4.0096	3.7715
	G_CV	44.5	51.6
PTF	N	54	54
	Mean	0.77	0.62
	SD	0.31	0.33
	GeoM	0.71	0.55
	G_CV	41.7	55.5
R (coefficient of correlation)	N	54	54
	Min	-1.000	-1.000
	Med	-0.994	-0.994
	Max	-0.863	-0.891
t_{1/2} [h]	N	54	54
	Mean	29.18	29.92
	SD	8.35	9.61
	GeoM	28.16	28.65
	G_CV	26.7	29.4
t_{max} [h]	N	54	54
	Mean	6.67	10.11
	SD	6.20	8.37
	CV	93.0	82.8
	Min	0.00	0.00
	Med	4.00	8.00
	Max	24.00	24.00
T_{cav} [h]	N	54	54
	Mean	10.42	10.52
	SD	1.69	2.14
	CV	16.2	20.3
	Min	7.24	5.32
	Med	10.27	10.41
	Max	15.05	16.34

a: multiple doses of 2.8 g TEST/day and **b:** multiple doses of 2.8 g REFERENCE/day (84 mg oxybutynin/day)

Table 4.2.1.3. Summary of PK Parameters for N-Desethoxybutynin: Treatment A: New Formulation ^{(b) (4)} and treatment B: Old (reference) formulation ^{(b) (4)} ^{(b) (4)} (Study SCO 5432)

Variable	Stat.	a	b
AUC_T [ng/ml*h]	N	54	54
	Mean	157.7218	139.4513
	SD	88.6001	84.0210
	GeoM	137.7699	119.5782
	G_CV	55.3	59.5
C_{av} [ng/ml]	N	54	54
	Mean	6.5717	5.8105
	SD	3.6917	3.5009
	GeoM	5.7404	4.9824
	G_CV	55.3	59.5
C_{max} [ng/ml]	N	54	54
	Mean	8.9495	7.2829
	SD	5.3402	4.2883
	GeoM	7.6858	6.2690
	G_CV	59.2	58.9
C_{min} [ng/ml]	N	54	54
	Mean	4.6255	4.4706
	SD	2.6520	2.8876
	GeoM	4.0281	3.7590
	G_CV	56.0	63.8
PTF	N	54	54
	Mean	0.64	0.50
	SD	0.23	0.21
	GeoM	0.59	0.46
	G_CV	40.3	44.0
R (coefficient of correla- tion)	N	54	54
	Min	-1.000	-1.000
	Med	-0.996	-0.996
	Max	-0.872	-0.882
t_{1/2} [h]	N	54	54
	Mean	31.17	31.42
	SD	8.42	12.62
	GeoM	30.11	29.88
	G_CV	27.0	30.1
t_{max} [h]	N	54	54
	Mean	7.97	11.78
	SD	4.44	9.33
	Min	0.00	0.00
	Med	8.00	8.00
	Max	24.00	24.00
T_{Cav} [h]	N	54	54
	Mean	10.79	11.65
	SD	1.55	2.13
	Min	6.96	6.82
	Med	10.63	11.44
	Max	13.61	17.37

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

In addition, the 90% CI for both the parent and the metabolites are not within 80% to 125% bioequivalence limits (Tables 4.2.1.4 and 4.2.1.5).

Table 4.2.1.4. Oxybutynin 90% Confidence Intervals (CI) (Study SCO 5432)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{av}	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 _{1/2}	ANOVA	log	a/b	98.33	91.76	105.37	21.7
T _{Cav}	ANOVA	lin	a-b	-0.09	-0.73	0.54	18.8
t _{max}	HAUSCHKE	lin	a-b	-4.00	-6.00	-1.00	

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

Table 4.2.1.5. N-Desethyloxybutynin 90% Confidence Intervals (CI) (Study SCO 5432)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{av}	ANOVA	log	a/b	115.43	106.10	125.58	26.6
C _{max}	ANOVA	log	a/b	122.90	112.63	134.10	27.5
C _{min}	ANOVA	log	a/b	107.22	97.40	118.03	30.5
PTF	ANOVA	log	a/b	130.36	116.11	146.36	37.1
t _{1/2}	ANOVA	log	a/b	101.20	94.73	108.11	20.7
T _{Cav}	ANOVA	lin	a-b	-0.86	-1.43	-0.29	15.1
t _{max}	HAUSCHKE	lin	a-b	-4.00	-6.02	-0.01	

a: multiple doses of 2.8 g TEST/day and b: multiple doses of 2.8 g REFERENCE/day

Reviewer's Comments:

Based on the ratios of C_{max}, AUC, and average concentrations, the exposure is approximately 15% to 23% higher after the new formulation compared to the old formulation for both oxybutynin and its metabolite, DEO (Tables 4.2.1.4 and 4.2.1.5). This difference may not be of clinical significance that may impose safety concern (see also Medical Officer's review).

However, based on this study, it can be concluded that the two formulations are **not** bioequivalent from the clinical pharmacology perspective. The C_{max} and AUC for both oxybutynin and DEO were outside the established bioequivalence limits of 80% to 125%. It should be noted that, except C_{max}, the 90% CI for AUC was slightly outside the limit (126.45% for oxybutynin and 125.58 for DEO).

Since the exposure after the new formulation (b) (4) (Treatment A) is higher than that of the old formulation (b) (4) (treatment B) and the drug was found relatively safe at the proposed dose of 84 mg (see medical officer's review), the inclusion of the 130 patients from the Phase III study who have been treated with the old formulation is acceptable from the clinical pharmacology perspective. The reason for the inclusion of

the 130 patients in the analysis of the data is to improve the statistical power of the trial to establish the efficacy of the treatment with the new oxybutynin gel.

However, it should be emphasized that from the clinical pharmacology perspective that **the two formulations are not bioequivalent.**

4.2.2 Study # 1034-PhII or SCO 5241 (Dose Escalation)

Study Title: A Phase II, Single-Center, Open-Label, Parallel, Three-Treatment, Dose-Ranging, Single-Period, Randomized, Single and Multiple-Dose Pharmacokinetic Study of Oxybutynin Gel in Healthy Volunteers

Objectives: To evaluate single-dose and multiple-dose pharmacokinetics and safety profiles of Oxybutynin Gel 3%, in doses of 42 mg, 60 mg and 84 mg oxybutynin/day after 20 days of consecutive topical application.

Study Design: This was three-treatment, single-period, randomized, single and multiple-dose design in 48 healthy males and females subjects (**Tables 4.2.2.1A and B and 4.2.2.2**). The study was designed as parallel group with 16 subjects with at least 70% females in each group as follows:

Table 1. 4.2.2.1 A Treatment Regimens (Study 1034-PhII)

Treatment a:	A single daily dose of 1.4 g of TEST ^a (42 mg oxybutynin), administered each morning for 20 consecutive days
Treatment b:	A single daily dose of 2 g of TEST (60 mg oxybutynin), administered each morning for 20 consecutive days
Treatment c:	A single daily dose of 2.8 g of TEST (84 mg oxybutynin), administered each morning for 20 consecutive days

^a – TEST – oxybutynin gel 3% Batch No. Oxyg146-03B/P1

Table 1. 4.2.2.1 B. Days of Dosing (Study 1034-PhII)

Table 4: Days of dosing

Treatment Group	Dose	Abdominal Skin Area	Time of Dose	Days
a	42 mg	350cm ²	08:00h	2 through 21
b	60 mg	500 cm ²	08:00h	2 through 21
c	84 mg	700 cm ²	08:00h	2 through 21

Table 1. 4.2.2.2 Subjects Demographic Information (Study 1034-PhII)

Table 6: Demographic data (n = 48)					
Subject	Sex	Age[year]	Weight [kg]	Height [cm]	BMI [kg/m²]
N	all	48	48	48	48
Mean		34.8	67.58	171.21	22.94
SD		8.4	11.04	9.05	2.19
Minimum		19	47.0	150.0	20.0
Maximum		53	93.0	196.0	27.8
N	male	12	12	12	12
Mean		37.0	80.42	182.17	24.19
SD		7.6	10.15	8.13	2.29
Minimum		23	60.0	172.0	20.3
Maximum		48	93.0	196.0	27.8
N	female	36	36	36	36
Mean		34.0	63.31	167.56	22.52
SD		8.7	7.48	5.85	2.02
Min		19	47.0	150.0	20.0
Max		53	84.0	178.0	27.8

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 as follows:

day 2: 00:00 (prior to 1st dosing); 02:00; 04:00; 08:00; 12:00; 16:00, 20:00
 day 3-20: 24:00 and every 24 hours trough levels
 day 21: 00:00 (prior to 20th dosing); 02:00; 04:00; 08:00; 12:00; 16:00, 20:00
 day 22: 24:00; 36:00
 day 23: 48:00
 day 24: 72:00
 day 25: 96:00
 day 26: 120:00 hours after dosing on day 21

The total amount of blood to that was collected for analysis of oxybutynin and DEO was approximately 342 ml (38 blood sampling points/9ml per sample). Oxybutynin and DEO were analyzed by a validated LC-MS/MS method.

Results:

There was increase in plasma concentration of oxybutynin with increase in dose (Figures 4.2.2.1-4.2.2.2 and Tables 4.2.2.3-). However, there was no clear dose proportionality for C_{max} and AUC, especially during the last dose (20th dose) on Days 21-22 that corresponds to 456-504 hours post first dose (Figure 4.2.2.3) and mean C_{max} at steady state (Figure 4.2.2.4)

Figure 4.2.2.1. Mean Oxybutynin Plasma Concentration-Time Profiles (Study 1034-PhII)

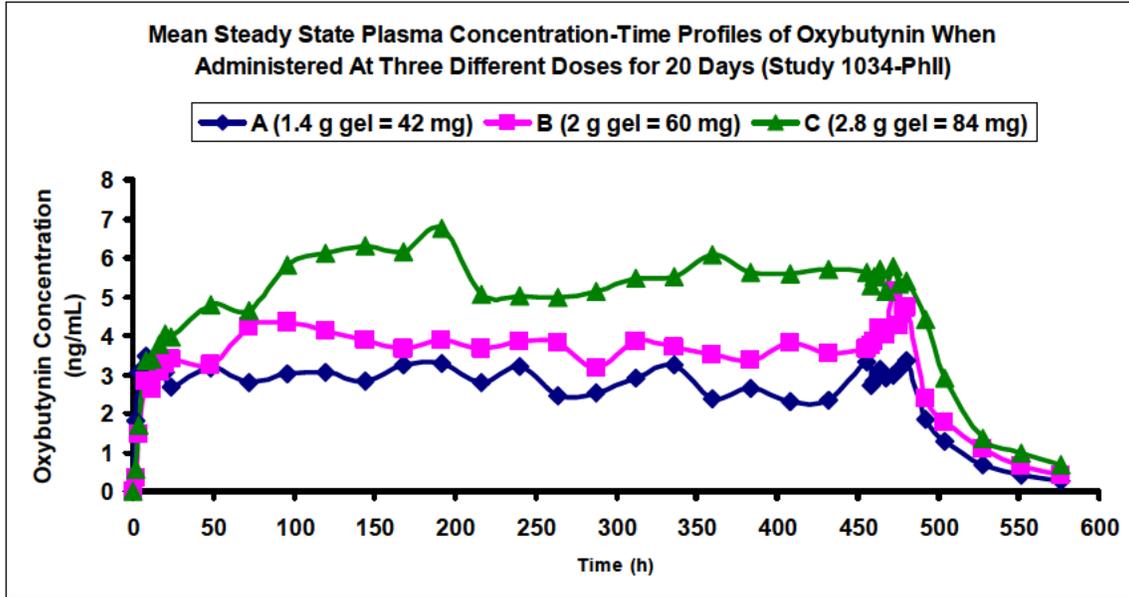


Figure 4.2.2.2. Mean Oxybutynin AUC (0-∞) in All Subjects (Study 1034-PhII)

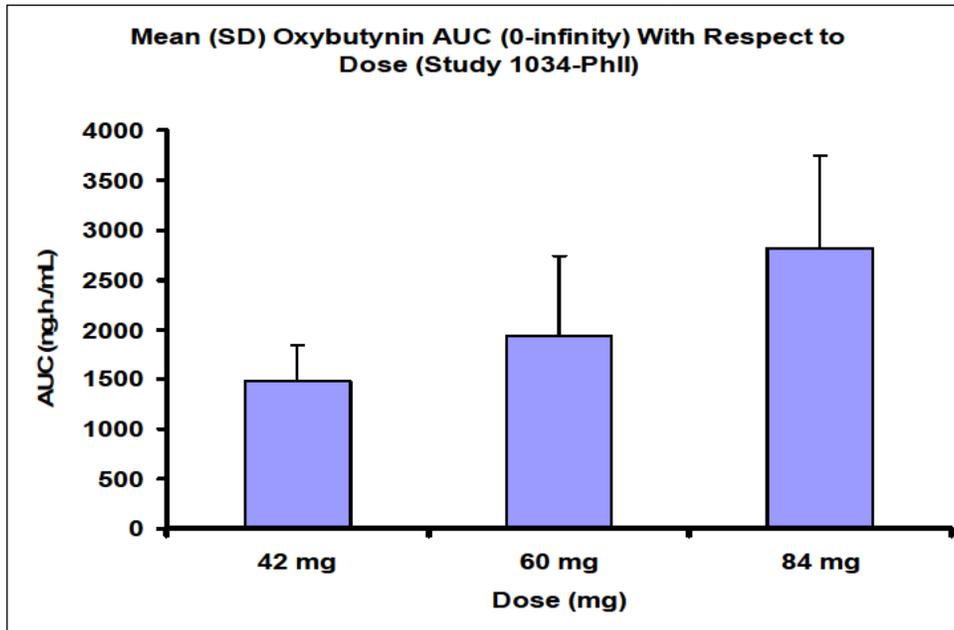


Figure 4.2.2.3. Mean Oxybutynin Plasma Concentration-Time Profiles after the 20th Dose on Days 21-22 (i.e., 456-504 h post first dose) (Study 1034-PhII)

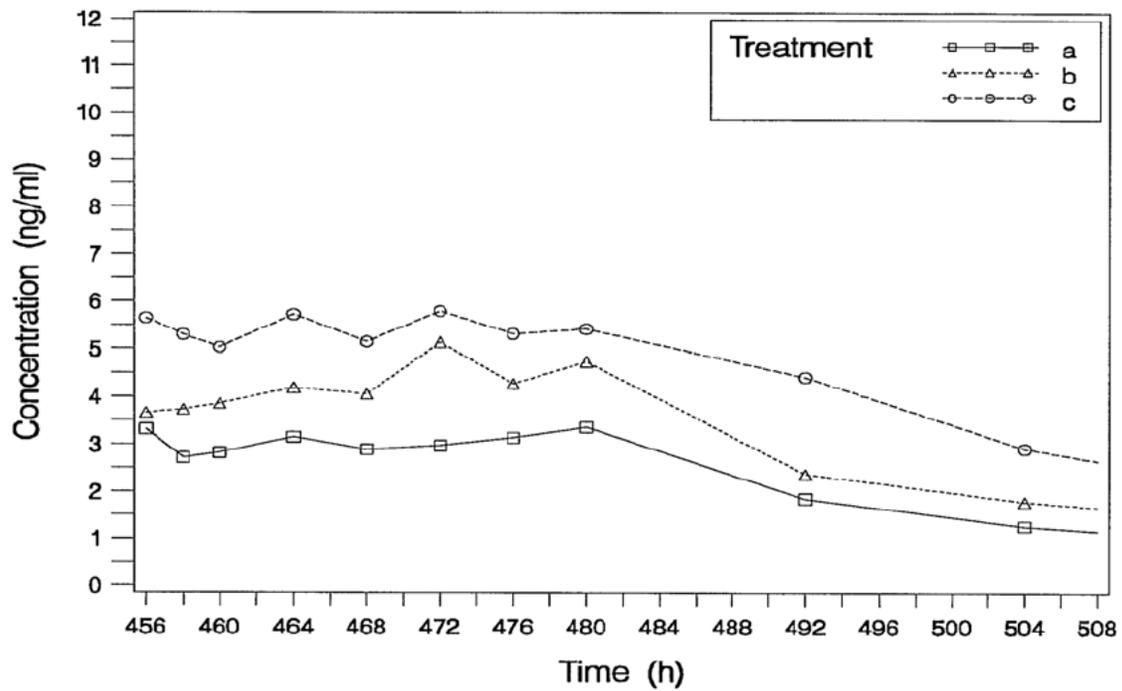


Figure 4.2.2.4. Mean Oxybutynin C_{max} and steady State in All Subjects (Study 1034-PhII)

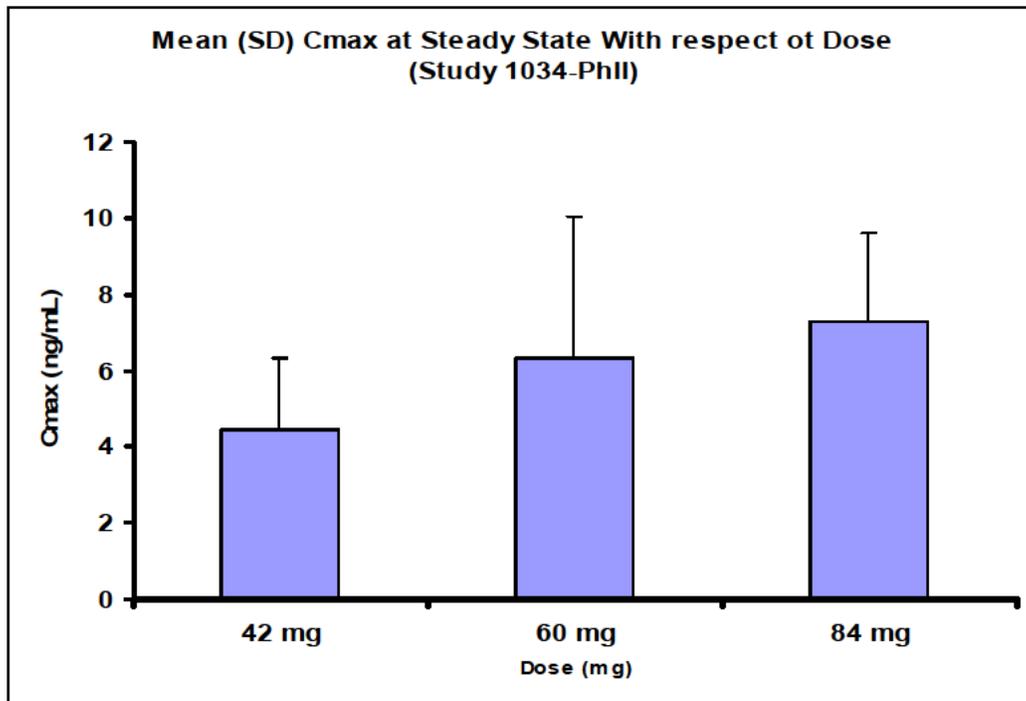


Table 1. 4.2.2.3. Summary of Oxybutynin PK Parameters (Study 1034-PhII)

Dose ^a	Statistic	AUC _{T=0,24} ^{sd} [ng/ml*h]	AUC _{T=0,24} ^{ss} [ng/ml*h]	C _{avg,sd} [ng/ml]	C _{av,ss} [ng/ml]	C _{max,sd} [ng/ml]	C _{max,ss} [ng/ml]	MR _{sd}	MR _{ss}
1.4 g (45 mg)	N	16	16	16	16	16	16	16	16
	MEAN	70.52	72.51	2.938	3.021	5.193	4.445	1.018	1.007
	SD	103.17	24.27	4.299	1.011	8.417	1.898	0.199	0.307
	Geo_M	46.65	68.95	1.944	2.873	3.279	4.111	0.998	0.961
	(Geo_CV)	92.0	33.6	92.0	33.579	93.6	41.9	21.486	33.112
2 g (60 mg)	N	16	16	16	16	16	16	16	16
	MEAN	58.95	102.80	2.456	4.283	4.001	6.334	1.105	1.007
	SD	59.59	56.72	2.483	2.363	3.393	3.696	0.289	0.404
	Geo_M	41.76	92.11	1.740	3.838	2.961	5.458	1.072	0.918
	Geo_CV	99.99	49.05	99.989	49.049	95.341	61.107	25.183	50.686
2.8 g (84 mg)	N	16	16	16	16	16	16	16	16
	MEAN	71.88	130.08	2.995	5.420	4.752	7.304	1.070	1.240
	SD	27.32	38.31	1.138	1.596	1.786	2.284	0.230	0.430
	Geo_M	66.94	124.61	2.789	5.192	4.428	6.959	1.047	1.180
	Geo_CV	41.48	31.76	41.483	31.765	41.149	33.727	21.828	32.420

^a dose as g gel (mg oxybutynin). AUC_{sd,0-24} – area under the plasma concentration-time curve, single dose; AUC_{ss,0-24}: area under the plasma concentration-time curve, steady-state; C_{avg,sd} - average concentration, single dose; C_{av,ss} -- average concentration, steady-state; C_{max,sd} - maximum observed plasma concentration, single dose; C_{max,ss} - maximum observed plasma concentration, single dose; MR_{sd} – ratio N-desethyloxybutynin/oxybutynin, single dose; MR_{ss} ratio N-desethyloxybutynin/oxybutynin, steady-state

Table 1. 4.2.2.4. Mean AUC 0-∞) Per Treatments and Gender: A= 42 mg, B = 60 mg, and C = 84 mg (Study 1034-PhII)

Treatment	Sex	Stat	AUC _{0-tz} [ng/ml*h]	AUC _{0-∞} [ng/ml*h]	rAUC [%]
a	all	N	16	16	16
		MEAN	1467.68	1479.30	0.7
		SD	361.44	367.42	0.6
		GeoM	1421.11	1431.64	0.5
		Geo_CV	27.99	28.22	100.8
a	f	N	12	12	12
		MEAN	1497.97	1509.37	0.7
		SD	405.73	413.18	0.6
		GeoM	1439.53	1449.40	0.5
		Geo_CV	31.92	32.23	106.8
a	m	N	4	4	4
		MEAN	1376.82	1389.12	0.9
		SD	186.87	185.99	0.8
		GeoM	1367.25	1379.65	0.7
		Geo_CV	13.73	13.62	88.4
b	all	N	16	16	16
		MEAN	1914.19	1934.41	1.1
		SD	797.05	800.86	1.0
		GeoM	1753.84	1772.64	0.7
		Geo_CV	47.26	47.33	119.4
b	f	N	12	12	12
		MEAN	2006.15	2025.69	1.0
		SD	878.20	881.19	0.9
		GeoM	1810.46	1828.77	0.7
		Geo_CV	53.49	53.51	108.1
b	m	N	4	4	4
		MEAN	1638.32	1660.57	1.2
		SD	461.78	475.84	1.1
		GeoM	1594.38	1614.37	0.8
		Geo_CV	26.78	27.33	197.4

Treatment	Sex	Stat	AUC _{0-tz} [ng/ml*h]	AUC _{0-∞} [ng/ml*h]	rAUC [%]
c	all	N	16	16	16
		MEAN	2794.49	2825.75	1.2
		SD	916.81	915.24	1.0
		GeoM	2669.92	2702.27	0.9
		Geo_CV	31.33	31.04	97.0
c	f	N	12	12	12
		MEAN	2597.74	2631.20	1.3
		SD	715.36	718.98	1.1
		GeoM	2511.62	2544.77	1.0
		Geo_CV	27.48	27.40	98.4
c	m	N	4	4	4
		MEAN	3384.76	3409.39	0.9
		SD	1306.49	1298.98	0.7
		GeoM	3207.24	3235.74	0.7
		Geo_CV	38.97	38.30	102.5

Considering the high variability in the data, overall the AUC was comparable in females and males (Table 4.2.2.4). However, the exposure was slightly higher in females at the first two doses of 42 and 60 mg, but it was in reversed order at the higher dose of 84 mg in which males were slightly higher than females (Figures 4.2.2.4-4.2.2.6 and Table 4.2.2.4-4.2.2.7).

Figure 4.2.2.4. Mean Oxybutynin Plasma Concentration-Time Profiles in Females and Males after Treatments A with 42 mg Dose (Study 1034-PhII)

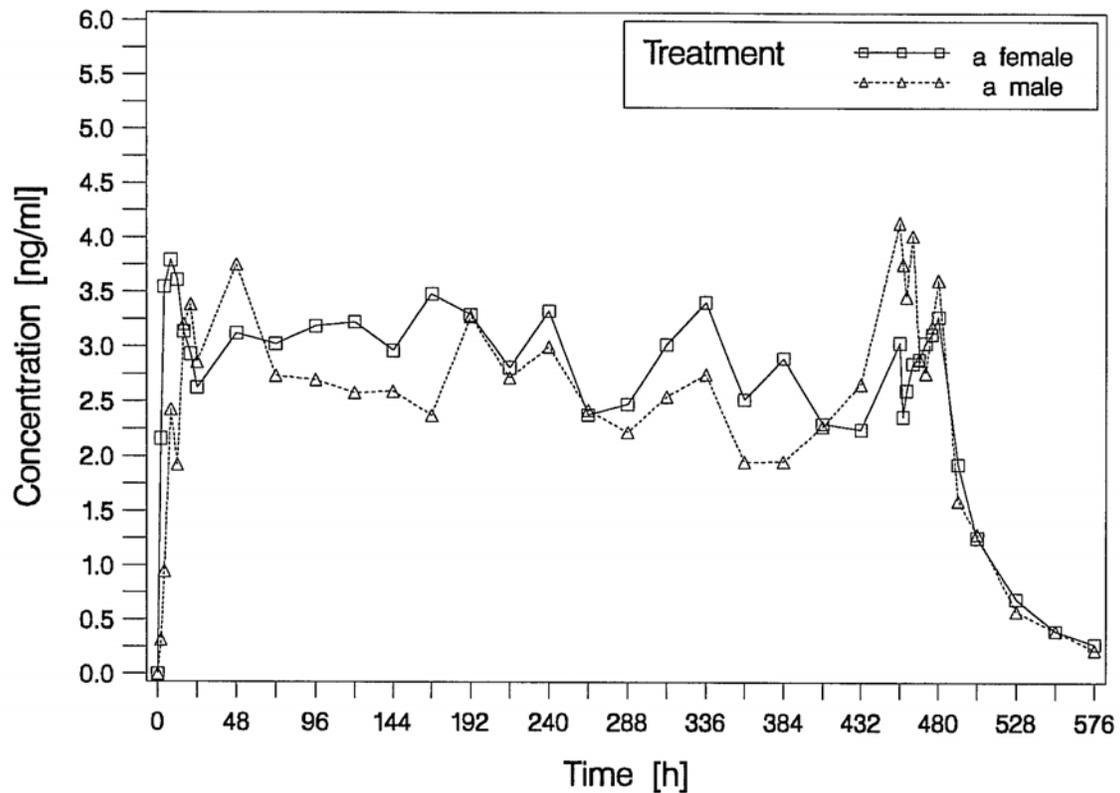


Figure 4.2.2.5. Mean Oxybutynin Plasma Concentration-Time Profiles in Females and Males after Treatments B with 60 mg Dose (Study 1034-PhII)

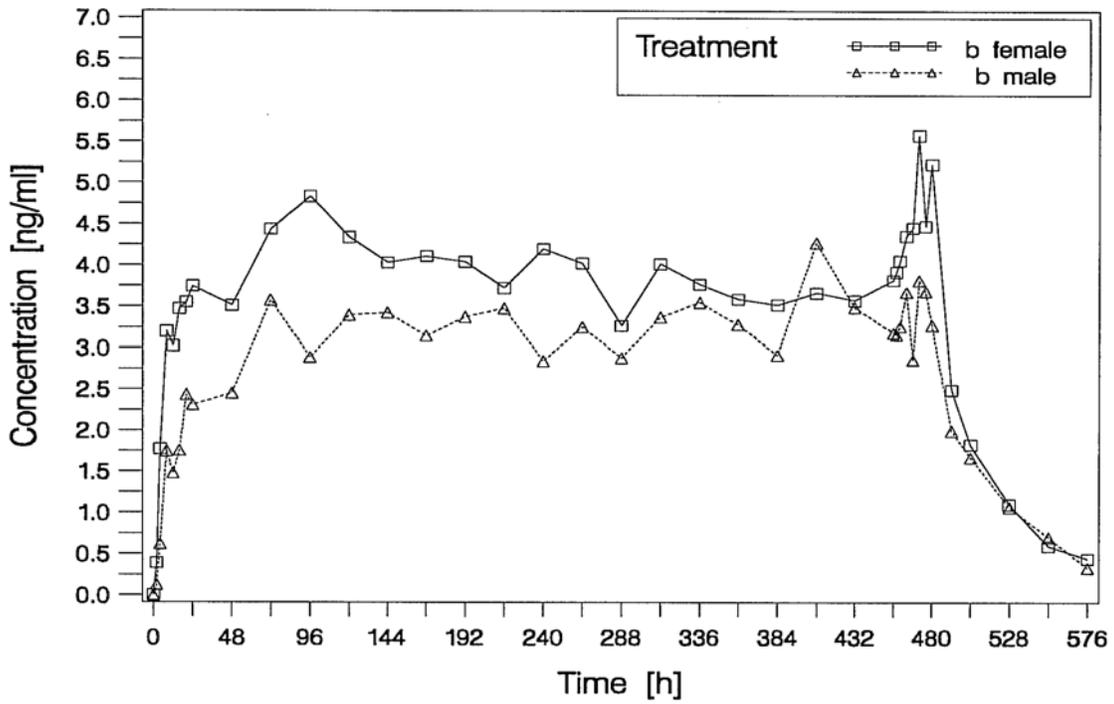
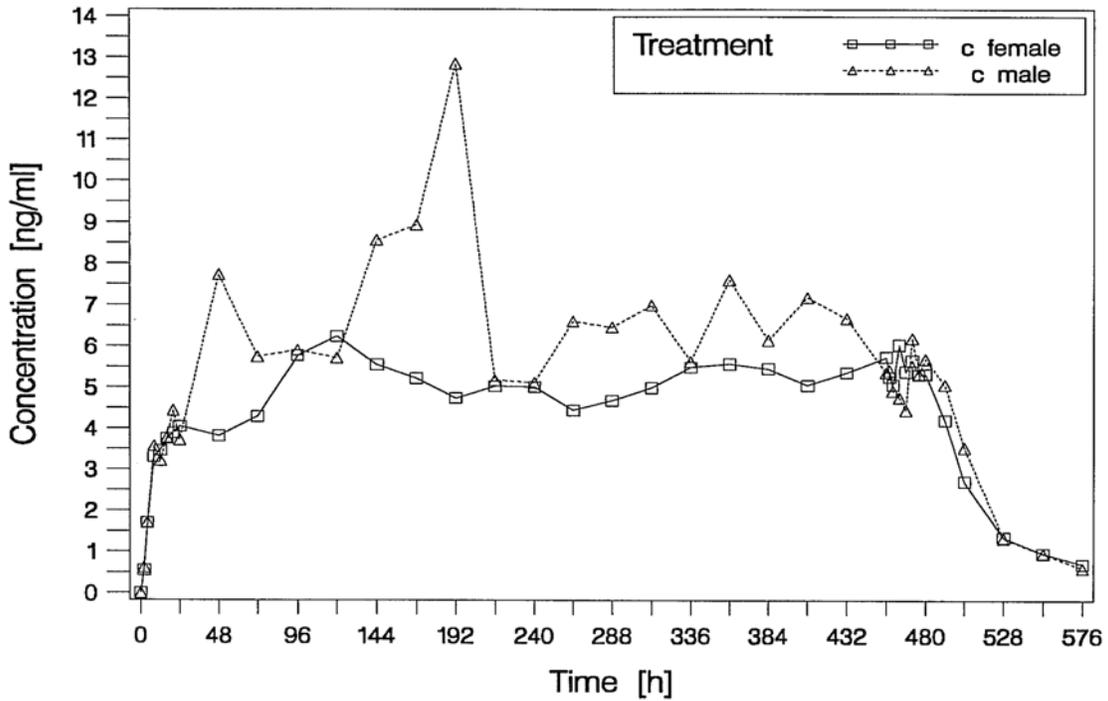


Figure 4.2.2.6. Mean Oxybutynin Plasma Concentration-Time Profiles in Females and Males after Treatments C with 84 mg Dose (Study 1034-PhII)



**Table 1. 4.2.2.5 Summary of Oxybutynin PK Parameters by Treatments and Sex
Treatment A = 42 mg (Study 1034-PhII)**

Sex	Stat	AUC _{1,ss,24} [ng/ml*h]	AUC _{1,ss,24} [ng/ml*h]	C _{av,ss} [ng/ml]	C _{max,ss} [ng/ml]	C _{max,ss} [ng/ml]	t _{max,ss} [h]	t _{max,ss} [h]	C _{min,ss} [ng/ml]	AUC _{1,ss,24} / AUC _{1,ss,24}	C _{max,ss} / C _{max,ss}	t _{max,ss} - t _{max,ss}	t _{1/2} [h]
f, m	N	16	16	16	16	16	16	16	16	16	16	16	16
	MEAN	70.52	72.51	3.021	5.193	4.445	16.37	11.75	2.219	1.84	1.62	-4.62	28.79
	SD	103.17	24.27	1.011	8.417	1.898	5.95	9.96	0.990	1.24	1.13	11.26	9.39
	Geom	46.65	68.95	2.873	3.279	4.111			2.015	1.48	1.25		27.56
	Geo_CV	92.0	33.6	33.579	93.6	41.9			49.1	88.41	100.6		30.34
f	N	12	12	12	12	12	12	12	12	12	12	12	12
	MEAN	76.37	69.76	2.907	5.725	4.338	15.49	12.33	2.097	1.81	1.59	-3.16	27.09
	SD	118.32	25.84	1.077	9.688	2.202	6.39	10.30	1.051	1.34	1.26	12.29	7.44
	Geom	47.04	65.96	2.748	3.320	3.914			1.876	1.40	1.18		26.19
	Geo_CV	104.22	35.29	104.218	107.961	48.327			52.897	98.86	114.75		27.60
m	N	4	4	4	4	4	4	4	4	4	4	4	4
	MEAN	52.96	80.75	3.365	3.599	4.768	19.00	10.00	2.584	1.95	1.68	-9.00	33.88
	SD	36.70	19.41	0.809	2.357	0.205	3.83	10.07	0.781	1.01	0.74	6.83	13.86
	Geom	45.50	78.74	3.281	3.157	4.764			2.494	1.73	1.51		32.13
	Geo_CV	66.67	27.40	66.673	27.402	4.357			31.624	64.01	64.97		37.18

**Table 1. 4.2.2.6 Summary of Oxybutynin PK Parameters by Treatments and Sex
Treatment A = 60 mg (Study 1034-PhII)**

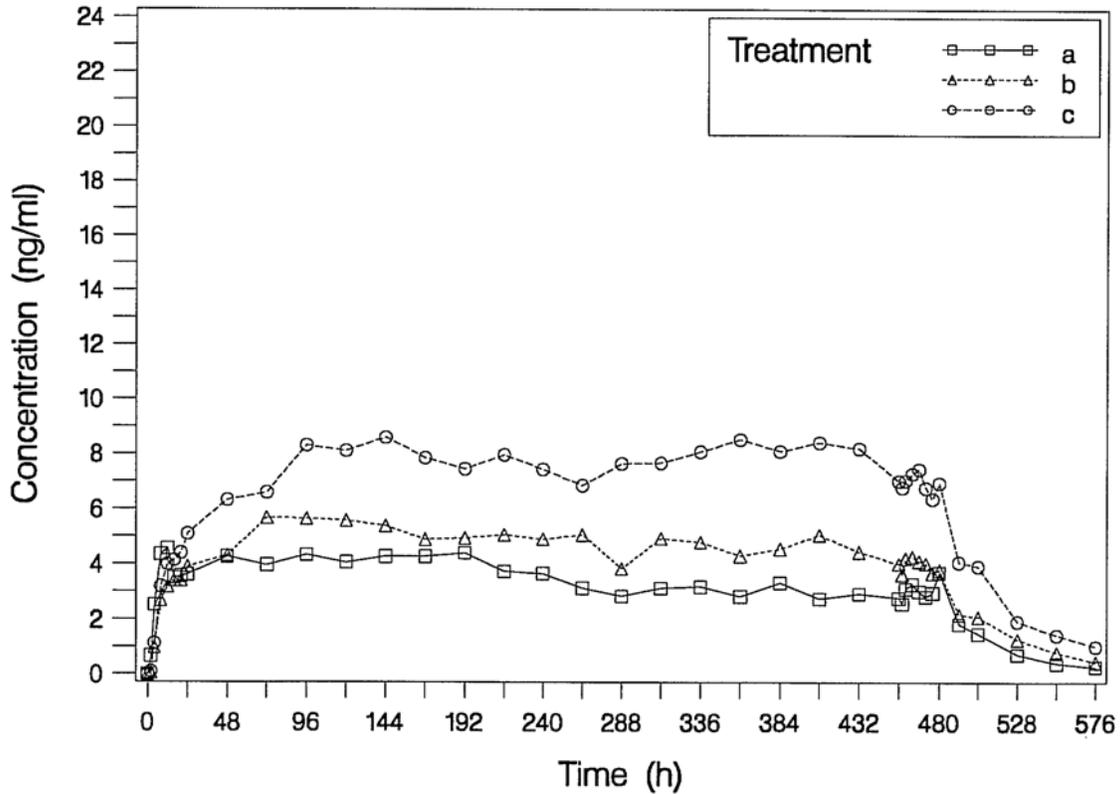
Sex	Stat	AUC ₀₋₂₄ [ng/ml ^h]	AUC ₀₋₂₄ [ng/ml ^h]	C _{av,ss} [ng/ml]	C _{max,ss} [ng/ml]	t _{max,ss} [h]	C _{min,ss} [ng/ml]	AUC ₀₋₂₄ [ng/ml ^h]	C _{max,ss} [ng/ml]	t _{max,ss} [h]	C _{max,ss} [ng/ml]	C _{max,ss} [ng/ml]	t _{max,ss} [h]	t _{1/2} [h]
f, m	N	16	16	16	16	16	16	16	16	16	16	16	16	16
	MEAN	58.95	102.80	4.283	4.001	6.334	3.010	2.67	2.30	15.76	3.010	2.30	-2.74	31.59
	SD	59.59	56.72	2.363	3.393	3.696	1.606	2.05	1.74	7.93	1.606	1.74	6.94	10.95
	Geom	41.76	92.11	3.838	2.961	5.458	2.721	2.21	1.84		2.721	1.84		29.80
	Geo_CV	99.99	49.05	49.049	95.341	61.107	46.527	66.02	75.46			75.46		36.97
f	N	12	12	12	12	12	12	12	12	12	12	12	12	12
	MEAN	66.58	109.69	4.570	4.469	7.035	3.096	2.78	2.52	15.34	3.096	2.52	-2.65	31.26
	SD	67.48	63.14	2.631	3.819	3.961	1.812	2.36	1.96	6.04	1.812	1.96	6.87	11.18
	Geom	44.43	96.90	4.038	3.129	6.053	2.743	2.18	1.93		2.743	1.93		29.45
	Geo_CV	120.68	54.05	54.055	115.134	64.410	52.306	77.37	88.51			88.51		37.92
m	N	4	4	4	4	4	4	4	4	4	4	4	4	4
	MEAN	36.07	82.12	3.422	2.596	4.232	2.750	2.35	1.65	20.03	2.750	1.65	-3.02	32.58
	SD	11.41	26.65	1.111	0.767	1.710	0.857	0.60	0.49	3.25	0.857	0.49	8.23	11.80
	Geom	34.66	79.11	3.296	2.511	4.002	2.655	2.28	1.59		2.655	1.59		30.90
	Geo_CV	33.85	31.89	31.892	30.658	39.179	31.041	30.08	31.54			31.54		39.58

**Table 1. 4.2.2.7 Summary of Oxybutynin PK Parameters by Treatments and Sex
Treatment A = 84 mg (Study 1034-PhII)**

Sex	Stat	AUC _{1,0-24} [ng/ml*h]	AUC _{1,0-24} [ng/ml*h]	C _{av,ss} [ng/ml]	C _{max,ss} [ng/ml]	t _{max,ss} [h]	C _{min,ss} [ng/ml]	AUC _{1,0-24} /AUC _{1,0-24}	C _{max,ss} / C _{max,ss}	t _{max,ss} - t _{max,ss} [h]	t _{1/2} [h]
f, m	N	16	16	16	16	16	16	16	16	16	16
	MEAN	71.88	130.08	5.420	4.752	7.304	4.067	2.08	1.70	-6.86	33.23
	SD	27.32	38.31	1.596	1.786	2.284	1.429	1.02	0.64	10.33	10.35
	Geom	66.94	124.61	5.192	4.428	6.959	3.840	1.86	1.57	31.96	31.96
f	Geo_CV	41.48	31.76	31.765	41.149	33.727	36.419	52.99	44.72	28.41	28.41
	N	12	12	12	12	12	12	12	12	12	12
	MEAN	71.61	131.65	5.486	4.752	7.132	4.124	2.18	1.71	-7.65	33.67
	SD	28.38	38.00	1.583	1.789	1.888	1.490	1.11	0.70	10.02	10.35
m	Geom	66.30	127.12	5.297	4.428	6.909	3.901	1.92	1.56	32.46	32.46
	Geo_CV	44.10	27.64	27.636	42.012	26.744	35.414	58.27	49.62	27.48	27.48
	N	4	4	4	4	4	4	4	4	4	4
	MEAN	72.70	125.36	5.223	4.749	7.821	3.897	1.80	1.67	-4.50	31.93
m	SD	27.87	44.79	1.866	2.052	3.541	1.421	0.71	0.51	12.48	11.81
	Geom	68.90	117.38	4.891	4.428	7.110	3.662	1.70	1.61	30.48	30.48
	Geo_CV	38.88	47.63	47.626	45.232	57.371	45.150	40.45	33.01	35.24	35.24

The data for oxybutynin metabolite, DEO follows the same trend as the parent drug in terms of exposure characteristic with dose (**Figure 4.2.2.8**). In addition, considering the high variability in the data, the exposure in females and males is comparable.

Figure 4.2.2.8. Mean DEO Plasma Concentration-Time Profiles (Study 1034-PhII)



Reviewer's Comments:

Overall, it appears that the increase in oxybutynin dose does not necessarily be associated with increase in exposure linearly. Thus, the absorption of oxybutynin may be limited by permeability factor rather than the dose. The same conclusion can be made for oxybutynin metabolite.

4.2.3 Study # SCO 5488 (Effect of Showering)

Study Title: A Phase I, single-center, multiple-dose, open-label, randomised, 4-period cross-over study to evaluate the effect of showering on the absorption of Oxybutynin from Anturol™ (Oxybutynin gel 3%)

Objectives: To assess the possible effect of showering at different times after multiple dosing of Oxybutynin gel 3% on the absorption of oxybutynin.

Study Design: This was a multiple dose study that was designed as a 4-way crossover in 11 healthy couples (i.e., 22 males and females) with no wash between treatment periods (Table 4.2.3.1). Prior to the start of first period, subjects received 84 mg dose of the gel on the abdomen for 3 days. Following the three days treatment subjects received the following additional 4 days treatments to ensure steady-state conditions:

Treatment A: 4 further application of 84 mg Oxybutynin on the abdomen and **not showering at all**

Treatment B: 4 further application 84 mg Oxybutynin on the abdomen and showering after **1 hour**

Treatment C: 4 further application 84 mg Oxybutynin on the abdomen and showering after **2 hour**

Treatment D: 4 further application 84 mg Oxybutynin on the abdomen and showering after **6 hours**

Blood samples:

Blood samples were collected over 24 hours after the fourth daily dose (i.e., Days 4 and Day 5) as follows:

Day 4: 00:00; 02:00; 04:00; 08:00; 12:00

Day 5*: 16:00; 24:00 hours after the fourth dosing

*day 5 corresponds to day 1 of the following study period

Table 4.2.3.1. Demographic Data

Ethnic origin	Gender	Stat.	Age [y]	Weight [kg]	Height [cm]	BMI [kg/m²]
white, N=22	female, N=9 male, N=13	N	22	22	22	22
		Mean	38.6	73.0	176.9	23.17
		SD	10.1	11.5	8.9	2.10
		CV	26.2	15.7	5.0	9.08
		Minimum	21	52	164	19.3
		Median	38.5	73.5	176.5	23.10
		Maximum	53	95	191	26.9
white, N=9	female	N	9	9	9	9
		Mean	37.6	64.7	170.1	22.28
		SD	11.8	8.0	5.4	2.01
		CV	31.4	12.3	3.2	9.01
		Minimum	21	52	164	19.3
		Median	43.0	66.0	170.0	21.70
		Maximum	53	75	180	25.6
white, N=13	male	N	13	13	13	13
		Mean	39.3	78.7	181.6	23.79
		SD	9.2	10.0	7.8	2.01
		CV	23.5	12.7	4.3	8.45
		Minimum	23	62	170	20.4
		Median	38.0	75.0	180.0	23.80
		Maximum	53	95	191	26.9

Results:

Overall, although there was high variability in the data, showering does not appear to affect the absorption of oxybutynin at the tested times in this study (**Figure 4.2.3. 1 and Table 4.2.3.2 and 4.2.3.3**).

Figure 4.2.3.1. Mean Plasma-Concentration-Time Profiles of Oxybutynin After Showering (Study #SCO 5488)

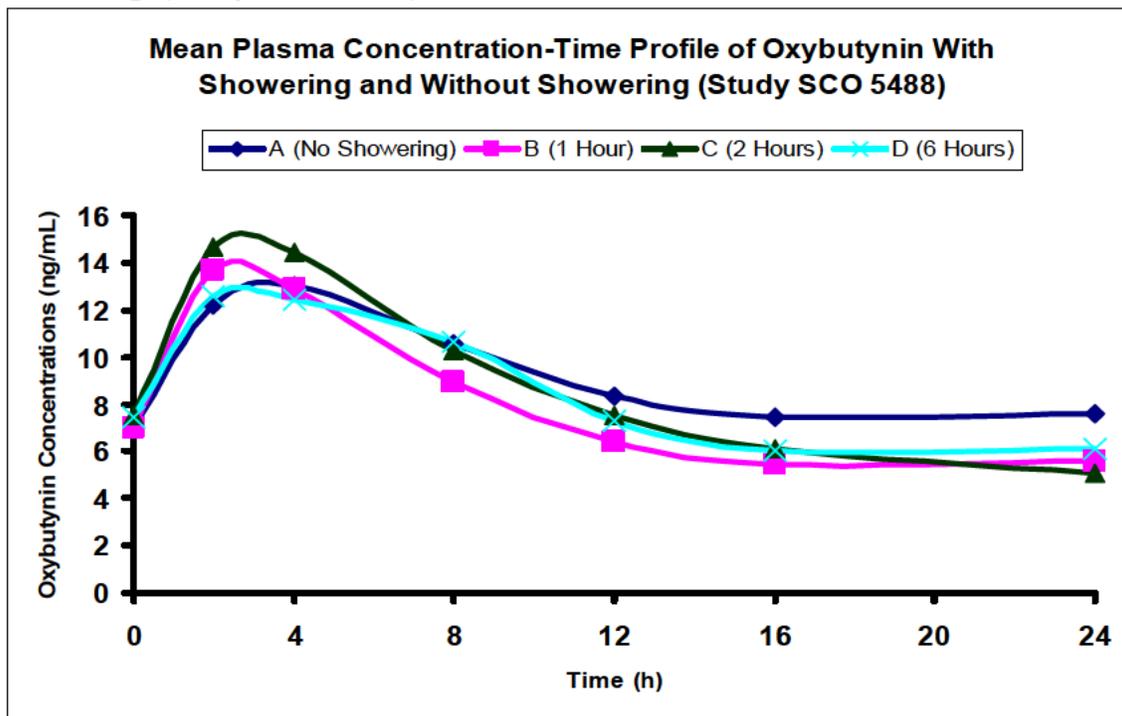


Table 4.2.3.2. Summary of PK Parameters of Oxybutynin After Showering (Study #SCO 5488)

Variable	Statistic	Treatment a	Treatment b	Treatment c	Treatment d
AUC _T [ng/ml*h]	N	22	22	22	22
	Mean	220.285	188.665	207.884	201.745
	SD	111.464	104.007	111.779	90.693
	GeoM	193.208	165.429	183.244	183.438
	G_CV	58.2	55.7	54.4	47.5
	N x>0	22	22	22	22
C _{max} [ng/ml]	N	22	22	22	22
	Mean	14.2875	15.1430	16.9040	15.0636
	SD	8.9758	11.6976	13.0003	9.4368
	GeoM	11.9575	11.9546	13.5876	12.8056
	G_CV	68.1	79.0	73.0	63.5
	N x>0	22	22	22	22

GeoM – geometric mean; G_CV – geometric coefficient of variation; N|x>0 – number of subjects with values above the limit of quantitation (LOQ). Treatments: a – no showering; b: showering 1 hr after application of Anturool; c: showering 2 hr after application; d: showering 6 hr after application.

Table 4.2.3.3. Oxybutynin 90% Confidence Intervals in the Effect of Showering Study (Study #SCO 5488)

PK-VARIABLE	METHOD	TRANS	COMP	PE [%]	LL [%]	UL [%]	ANOVA-CV [%]
AUC _T = C _{av}	ANOVA	log	b/a	85.23	76.99	94.36	20.3
			c/a	93.54	84.51	103.53	20.3
			d/a	94.06	84.99	104.11	20.3
C _{max}	ANOVA	log	b/a	98.81	87.26	111.90	25.0
			c/a	111.02	98.06	125.69	25.0
			d/a	105.86	93.51	119.85	25.0
t _{max}	TUKEY	lin	b-a	0.00	-1.00	0.00	
			c-a	0.00	-1.98	0.00	
			d-a	0.00	-1.00	1.00	

a: multiple doses of 2.8 g AnturoTM/day, no showering,
b: multiple doses of 2.8 g AnturoTM/day, showering after 1 hour,
c: multiple doses of 2.8 g AnturoTM/day, showering after 2 hours,
d: multiple doses of 2.8 g AnturoTM/day, showering after 6 hours,

Reviewer's Comments:

Based on this data, it is recommended that showering should be withheld until 1 hour has passed after the application of the gel. This statement or similar language should be included in the label.

4.2.4 Study # OXBTN/200/223 (Application Site)

Study Title: A Single Dose, Open-Label Comparative Three-Way, Application Site Cross Over PK Study of Oxybutynin Gel (3%) in Healthy Human Volunteers Fasting State

Objectives: To investigate the absorption and PK profiles of oxybutynin from three different application sites.

Study Design: This was 3-ways crossover in 25 healthy male and female subjects (**Table 4.2.3.1**) following 84 mg dose as follows:

Site A: Abdomen (reference site)

Site B: Inner and upper parts of upper thighs (test site)

Site C: Upper arms and shoulders (test site)

Table 4.2.3.1. Demographic Data and Study Schedule

	Group 1			Group 2		
	Females-17			Females-07		
	Males-06			Males-00		
Check-In Dates	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
	24/08/2006	04/09/2006	15/09/2006	08/09/2006	19/09/2006	03/10/2006
Dosing Dates	25/08/2006	05/09/2006	16/09/2006	09/09/2006	20/09/2006	04/10/2006

Blood samples were collected from each subject over 120 hours following each treatment (site).

Results:

It appears that the absorption from arms/shoulders is higher than the other two tested sites for both oxybutynin and its metabolite, DEO (**Figure 4.2.4.1 and 2.4.2.1 and Table 2.4.2.1**). It should be noted that there was wide variability in the data with %CV ranging from approximately 38% to 62% for both C_{max} and AUC following the three sites (**Table 2.4.2.1**)

Figure 2.4.2.1. Mean Plasma-Concentration-Time Profiles of Oxybutynin When Applied to Three Different Sites(Study #OXYTN/2006/223)

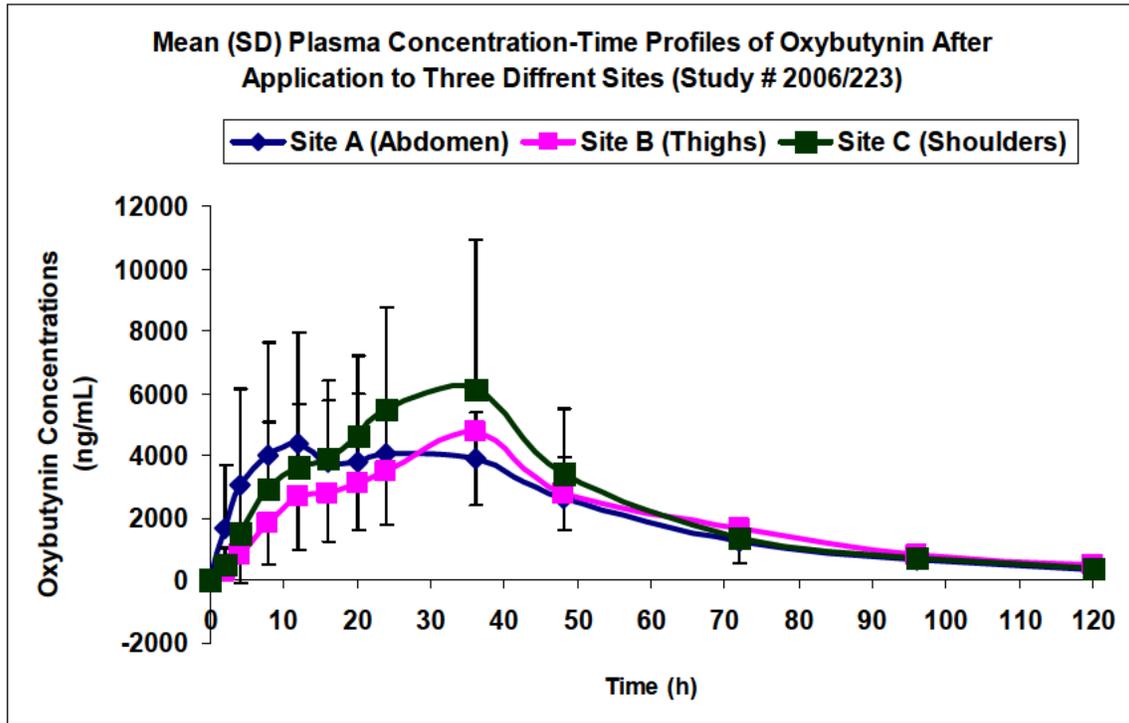


Figure 2.4.2.2. Mean Plasma-Concentration-Time Profiles of DEO When Applied to Three Different Sites (Study #OXYTN/2006/223)

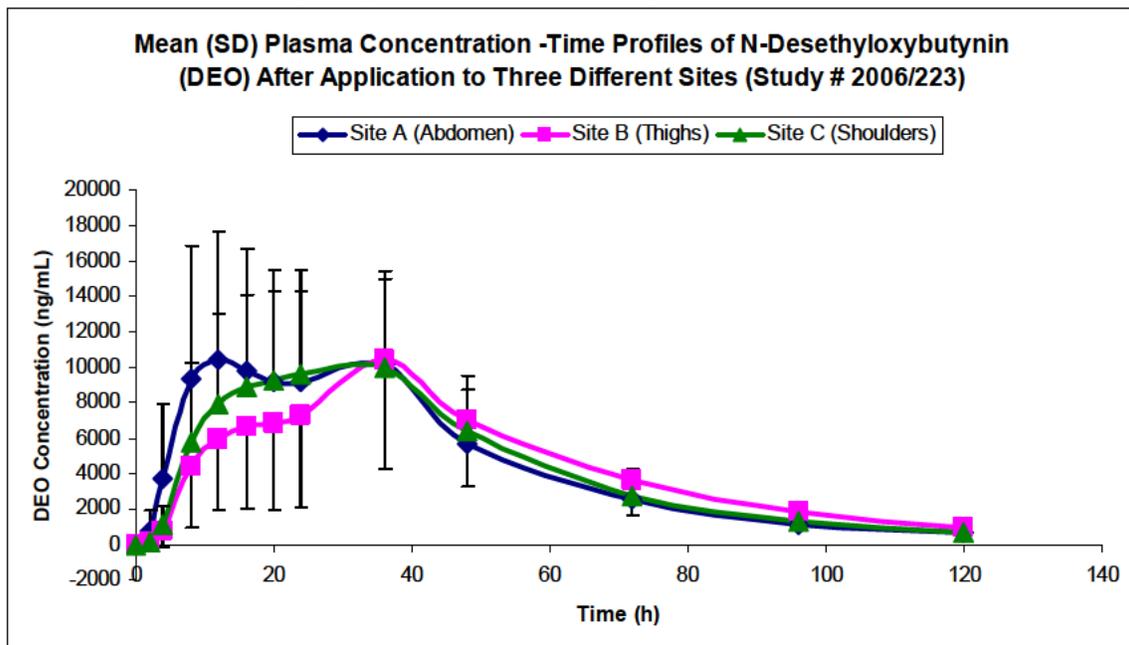


Table 2.4.2.1. Summary of Oxybutynin PK Parameters After Dose Normalization (Study #OXYTN/2006/223)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean \pm SD		
	Reference Site A (n=25)	Test Site B (n=25)	Test Site C (n=25)
$AUC_{(0-t)}$ (ng·h/mL)	265.758 (38.1) 284.096 \pm 108.17	262.925 (50.6) 286.918 \pm 145.25	302.841 (42.3) 329.051 \pm 139.06
$AUC_{(0-\infty)}$ (ng·h/mL)	280.944 (36.2) 297.776 \pm 107.69	285.036 (48.9) 309.990 \pm 151.68	316.573 (40.7) 342.316 \pm 139.36
C_{max} (ng/mL)	5.628 (55.8) 6.317 \pm 3.53	5.243 (45.1) 5.800 \pm 2.61	7.475 (62.3) 8.811 \pm 5.49
T_{max} (h)	24.00 (4.00 – 48.00)	36.00 (12.00 – 48.00)	24.00 (8.00 - 48.00)

Reviewers Comments:

Considering the variability in the data, it can be concluded that the absorption from the three sites is overall comparable.

4.3 Filing Memo:

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	202513	Brand Name	Anturol ®	
OCP Division (I, II, III, IV, V)	III	Generic Name	Oxybutynin	
Medical Division	DRUP	Drug Class	Muscarinic antagonist	
OCP Reviewer	Sayed (Sam.) Al Habet, R.Ph., Ph.D.	Indication(s)	Overactive Bladder	
OCP Secondary Reviewer/Signer	E. Dennis Bashaw, Pharm.D.	Dosage Form	3% gel	
Pharmacometrics Reviewer	N/A	Dosing Regimen	(b) (4) 84 mg (b) -3 pumps) once daily	
Date of Submission	December 17, 2010 (original pending user fee clarification) February 8, 2011 (accepted dated after user fee clarification)	Route of Administration	Topical (Abdomen, arms, or thighs)	
Estimated Due Date of OCP Review	September 2011	Sponsor	Antares Pharma, Ewing, NJ	
Medical Division Due Date	October 2011	Priority Classification	Standard	
PDUFA Due Date	December 8, 2011			
<i>Clin. Pharm. and Biopharm. Information</i>				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		X		
Table of Contents present and sufficient to locate reports, tables, data, etc.		X		
Tabular Listing of All Human Studies		X		
HPK Summary		X		
Labeling		X		
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology		X		
Mass balance:		N/A		
Isozyme characterization:		N/A		
Blood/plasma ratio:		N/A		
Plasma protein binding:		N/A		
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-				
single dose:		7		Studies: SCO-5432, 1034-PHII, OXBTN/2006/223, SCO 5486, SCO 5488, SCO 5487, and OXPk2)
multiple dose:		2		42 mg, 60 mg, and 84 mg/da x 20 days (Study # 1034-PhII), n=48 healthy subjects And Pilot study x 7 days (#OXPk2)
Patients-				
single dose:				
multiple dose:				

Dose proportionality -				
fasting / non-fasting single dose:		1		Dose escalation (Study # 1034-PhII)
fasting / non-fasting multiple dose:		1		Dose escalation (Study # 1034-PhII)
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				Across study comparison between efficacy and safety data from Study # 20070060 and data available in literature for marketed Oxytrol-TDS® and Gelnique®) in special population
ethnicity:		1		
gender:		1		
pediatrics:				
geriatrics:		1		
renal impairment:		1		
hepatic impairment:		1		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:		1		BE Study # SCO 5432 (old vs new formulation)
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
In vitro Penetration Studies		3		3 ex vivo penetration studies with pig, human cadaver, and fresh human skin (Studies # AP-1034, 368/03, and 932/09)
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			N/A	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			N/A	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			N/A	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			N/A	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			N/A	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			N/A	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the	X			

	label?				
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			N/A	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Reviewer's Comments:

- Originally this NDA was submitted on December 17, 2010. However, due to user fee issues, the filing date is considered February 8, 2011.
- This is a 505(b) (1) application for 3% gel containing oxybutynin packaged in a plastic container with a metered-dose pump for delivery.
- Reference products are Gelnique® sachet containing 1 gram (1.14 mL) gel for topical use and Oxytrol® Transdermal Delivery System.
- In summary, in addition to the double blind placebo controlled safety and efficacy study in approximately 600 patients at two doses of 56 mg and 84 mg for 12 weeks (Study # 2007/0060) the sponsor conducted the following PK studies:
 - BE for bridging the old and new formulation (not bioequivalent based on Cmax and AUC, Study # SCO 5432)
 - Multiple dose study at the following doses: 42 mg, 60 mg, and 84 mg per day (QAM) x 20 days (pivotal PK study # 1034-PhII)
 - Effect of site of application (abdomen, thighs, and arms/shoulders, Study # OXBTN/2006/223))
 - Partner transfer study (Study # SCO 5486)
 - Effect of showering (Study # SCO 5488)
 - Effect of sunscreen (Study # SCO 5487)
 - Pilot study (2 gram vs 1 gram gel per day x 7 days, Study # OXPK2)

In addition, the sponsor conducted **3 *ex Vivo*** penetration studies in pig, human cadaver, and fresh human skin. From the clinical pharmacology perspective, the data from these studies are of limited value and will not be part of the final decision making process for this application. Furthermore, the sponsor conducted across study analysis for the safety and efficacy of the gel compared to the marketed Gelnique® and Oxytrol-TDS®.

The sponsor had several meetings with the Agency to discuss the development program of the gel. Based on these meetings, it was decided that the best approaches for this NDA is to be filed under 505(b)(1) route. The most relevant meetings to the clinical pharmacology are the following:

- Pre-IND meeting held on February 9, 2005 (MM dated March 11, 2005, IND 70, 527)
- End of Phase II Meeting held on May 2, 2006 (MM dated May 31, 2006, IND 70,527)

- Responses dated October 22, 2009 (IND 70,527)
- Responses dated November 2, 2009 (IND 70,527)

Formulations:

The formulation was changed during Phase III safety and efficacy study (Study # 20070060). The rationale for the change in formulation is (b) (4)

(b) (4). According to the sponsor, during the study the sponsor decided to change the formulation. Therefore, 130 patients were exposed to the old formulation (b) (4) (old formulation) and 496 patients were exposed to the new formulation containing (b) (4) in their pivotal efficacy and safety study.

The list of other studies is shown in **Appendix 1**. In summary, the pilot (Study # OXPk2), dose-escalation (study # 1034-PhII), and site application (OXBTN 2006/223) studies were conducted with the old formulation (b) (4) whereas the effect of sunscreen (Study # SCO 5487), showering (Study # SCO 5488), and partner transfer (Study # SCO 5486) studies were conducted with the new formulation (b) (4) (**Appendix 1**).

Synopses of Individual Studies:

Study # OXPk2 (Pilot PK):

Objectives: 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%).

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 for 7 days.

The mean AUC increased from approximately 75 to 164 ng/mL.h and C_{max} 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).

Study # 1034-PhII (Dose Escalating Study):

Objective: To evaluate single-dose and multiple-dose PK and safety profiles of Oxybutynin Gel 3%, in doses of 42 mg, 60 mg and 84 mg oxybutynin/day after 20 days of consecutive topical application to the abdomen. The results from this study were used to select the dose in the phase III study.

Based on the preliminary review of the summary data, after 20 days of administration there was accumulation of both oxybutynin and N-desethyloxybutynine with accumulation ratio of 185% and 189%, respectively. There was no clear dose

proportionality in this study. Based on this study, the doses selected for Phase III study were 56 mg and 84 mg.

Study # OXBTN 2006/223 (Effect of Application Site):

Objectives: To determine the PK profiles after 84 mg single dose of oxybutynin gel in healthy subjects as follows:

Site A: Abdomen (reference site)

Site B: Inner and upper part of upper thighs

Site C: Upper arms and shoulders

The geometric mean for AUC was 265, 262, and 302 ng/mL.h and Cmax 5.6, 5.2, and 7.4 ng/mL for site A, B, and C, respectively. Overall, there is some differences in the sites in which arms and shoulders (site C) being higher than the other two sites. The sponsor's proposed label suggests alternating the gel application among these three sites.

Study SCO 5432 (BE Study):

Objectives of the BE Study (SCO 5432): To establish the bridge between the old formulation (b) (4) and the new formulation (b) (4) (to-be-marketed). The study was a single dose, crossover in 58 healthy subjects at 84 mg gel dose. State the site of application and what the results are.

The 90% CI for AUC is 106.28 and 126 and Cmax 111.88 and 136.83. Therefore, the two formulations are not bioequivalent.

Study SCO 5486 (Partner Transfer Study):

Objectives: To assess the potential transfer of oxybutynin from one subject treated with oxybutynin to his untreated partner through arm-to-arm contact by undressed or dressed arms. The study design is as follows:

Treatment A: Single dose of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on one arm of one partner. Two hours after treatment the partners underwent vigorous arm to arm contact for fifteen minutes with the treated arm is undressed. The untreated partner had a bare arm.

Treatment B: Single dose of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on one arm of one partner. Two hours after treatment the partners underwent vigorous arm to arm contact for fifteen minutes, whereas the treated arm is dressed. The untreated partner had a bare arm

From this study there was detectable levels of oxybutynine in undressed subjects with an over mean Cmax of 0.78 ng/ml and AUC of 12.2 ng/mL.h. However, no detectable levels was observed in the dressed subjects.

It should be noted that the C_{max} observed in this study (0.78 ng/mL) is approximately 10 folds lower than that observed in the site study (Study # OXBTN 2006/223) when the gel applied to upper arms and shoulders (mean C_{max} = 7.4 ng/mL). Although there was no detectable concentration in dressed subjects, patients are instructed in the sponsor's proposed label to cover the application area with clothing after application of the gel.

Study SCO 5487 (Effect of Sunscreen):

Objectives: To assess the possible effect of sunscreen, applied before or after the treatment of oxybutynin, on the absorption of oxybutynin. The study employed a single-center, single-dose, open-label, randomized, 3-period cross-over design with a wash-out phase of at least 14 days between treatment phases. The study design is as follows:

Treatment A: single dose of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen

Treatment B: single dose of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen, 30 min before application of sunscreen on the same skin area

Treatment C: single dose of 2.8 g gel (corresponding to 84 mg Oxybutynin, 700 cm² skin surface) on the abdomen, 30 min after application of sunscreen on the same skin area

There was no difference in the exposure (C_{max} and AUC) in the three treatments with and without sunscreen. The mean AUC was 151, 1689, and 154 ng/mL.h and C_{max} was 4.9, 6.1, and 4.4 ng/mL following treatments A, B, and C respectively. Based on this, the sponsor's proposed label states that sunscreen has no effect on the systemic exposure of oxybutynin.

Study SCO5488 (Effect of Showering):

Objectives: To assess the possible effect of showering at different times after multiple dosing of Oxybutynin gel on the absorption of oxybutynin.

Design: This study employed single-center, multiple-dose, open-label, randomized, 4-period cross-over design with no wash between treatment periods. Prior to start of the first treatment period the subjects received 2.8 g gel (84 mg Oxybutynin to 700 cm² skin surface) on the abdomen for 3 days. Over the next 4 days, subjects received each of the treatments summarized below:

Treatment A: 4 further administrations of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen and not showering at all

Treatment B: 4 further administrations of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen and showering after 1 hour

Treatment C: 4 further administrations of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen and showering after 2 hours

Treatment D: 4 further administrations of 2.8 g gel (84 mg Oxybutynin, 700 cm² skin surface) on the abdomen and showering after 6 hours

From this study, there was no observed difference in the exposure (C_{max} and AUC) among the four treatments arms after and before showering. The mean AUC was 220, 189, 208, and 202 ng/mL.h and C_{max} was 14.2, 15.1, 16.9, and 15.0 ng/mL following treatments A, B, C, and D respectively. Based on the data from this study, the sponsor's proposed label indicates that showering after one hour does not affect the overall systemic exposure to oxybutynin.

Clinical Study (2007/0060)

Objectives: To establish the safety and efficacy of oxybutynin 3% gel in patients with over active bladder.

Design:

This was a double-blind, randomized, 12-week clinical trial comparing the effects of 2 doses of oxybutynin gel (56 and 84 mg) to placebo in patients with urinary frequency urge and mixed urinary incontinence (UI) with a predominance of urge incontinence episodes and a 24-week open-label extension on 84 mg dose. Approximately 600 patients were randomized for this study as follows.

Group A: Oxybutynin (84 mg/day) daily topical application x 12 weeks

Group B: Oxybutynin (56 mg/day), daily topical application x 12 weeks

Group C: Matching placebo gel, daily topical application x 12 weeks

Formulations Used in Phase III Study:

As stated earlier, the formulation was changed during Phase III study (b) (4). Therefore, 130 patients received the old formulation (b) (4) and 496 patients received the new formulations (b) (4). The data has been reported for both formulations.

Based on the preliminary review of the summary of the data, the study demonstrates that 56 mg/day and 84 mg/day doses produced statistically significant reduction in the primary study endpoints as defined by the change from baseline in the number of urinary incontinence episodes per week (for details see Medical Officer's review).

Based on this study, the sponsor's proposed label indicates that patients who received oxybutynin experienced a greater improvement in symptoms compared with patients who received placebo. At week 12, median reductions (improvement) from baseline in weekly Urinary Incontinence Episodes (UIEs) were -18.7 (b) (4) episodes experienced by

patients in the oxybutynin 84 mg (b) (4), compared with -16.3 episodes in the placebo group.

Conclusions:

The sponsor conducted adequate studies to satisfy the clinical pharmacology program. Although, the two formulations (old) and to-be-marketed are not bioequivalent (Study # SCO 5432), the approvability of the NDA will be based on overall assessment of the PK data as well as the safety and efficacy data from Phase III study (Study # 20070060). At the time of filing this review, no DSI inspection is recommended.

From the clinical pharmacology perspective, the NDA can be filed.

Recommendation:

The NDA can be filed from the clinical pharmacology perspective. At this time, from the clinical pharmacology perspective, no DSI inspection is required.

Sayed (Sam) Al Habet, RP.h., Ph.D.

Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw, Pharm.D.

Secondary Reviewer/Supervisor Date

Appendix 1: Summary of Gel Formulations Used in Clinical Studies

Study No. Study Report Location	Formulation Number	Oxybutynin Content (%)	Batch Number(s)	Description of Change	Reason for change
OXPK2 (5.3.1.1-1)	(b) (4)	3	031101	NA	NA
1034-PhII (5.3.1.2-1)		3	Oxyg146-03B/P1	New Batch	NA
OXBTN/2006/223 (5.3.1.2)		3	C0900A001	New Batch	NA
SCO 5432 (5.3.1.2-2)		3	Oxvg 146-20B/P1 (b) (4) Oxvg 223-05B/P1 (b) (4)	New formulation (b) (4) for comparison with older formulation (b) (4)	Changed original formulation (b) (4)
SCO 5486 (5.3.1.1-4)		3	HKB	New Batch	NA
SCO 5487 (5.3.1.1-5)		3	HKB	NA	NA
SCO 5488 (5.3.1.1-3)		3	HKB	NA	NA
20070060 (5.3.5.1)		3	C0847B001	Initial Batch for Phase 3 Study (Anturol)	NA
		3	R0266B003	Batch for Phase 3 Study (b) (4)	
		3	HKB	Backup Batch for Phase 3 Study (b) (4)	
20070060 (5.3.5.1)		Placebo	C0846B001	Batch for Phase 3 Study (Placebo)	NA
		Placebo	R0267B002	Batch for Phase 3 Study (b) (4)	(b) (4)

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/s/

SAYED AL HABET
10/13/2011

MYONG JIN KIM
10/13/2011

ONDQA (Biopharmaceutics) Review

NDA: 202-513
Submission Date: 02/08/11; 7/22/2011
Product: Oxybutynin Gel, 3% (Anturol)
Type of Submission: Original NDA
Applicant: Antares Pharma, Inc.
Reviewer: Tapash K. Ghosh, Ph.D.

Submission: This original New Drug Application (NDA 202-513) is for Oxybutynin Gel, 3% (Proposed tradename Anturol™ (Oxybutynin Gel 3%). The proposed product is a transparent, fast-drying, colorless to slightly yellow, non-occlusive homogeneous gel, without particles containing 3.0% w/w oxybutynin free base. The gel is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Biopharmaceutics: This review is focused on the evaluation of the proposed in vitro diffusion method and the proposed acceptance criterion for this test.

Recommendation:

ONDQA - Biopharmaceutics evaluated the provided information and has the following comments:

- 1. It is not clear, why the document QUC-11-002 entitled “Anturol Diffusion Rate (Release rate) Development Report” was created on July 21, 2011, after receiving the IR from the Agency dated July 15, 2011. It raises some concern; please explain.*
- 2. A full review of the justification of the different parameters used during the development of the proposed in vitro diffusion/release method and the setting of the proposed specifications, cannot be made without evaluating the information addressing our outstanding questions listed in pages 5 and 6 of this review and to-be-sent to the Applicant in an Information Request Letter.*
- 3. In conclusion, at this point there are outstanding Biopharmaceutics questions that the Applicant needs to address before this NDA can be recommended for approval from the Biopharmaceutics point of view.*

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer

Signed by Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Biopharmaceutics Review

Drug Product Formulation:

The composition of the drug product, the quality standard and the function of each constituent of the drug product are presented in **Tables 1 and 2**.

Table 1 Components of Oxybutynin 3% Gel

Component and Grade	Regulatory/Safety Status	Function
Oxybutynin base	US DMF	Active Ingredient
Diethylene glycol monoethyl ether, NF (DGME) (b) (4)	USP/NF	(b) (4)
(b) (4)	USP/NF	
Hydroxypropyl cellulose (b) (4) NF	USP/NF	
Propylene glycol, USP	USP/NF	
Butylated hydroxytoluene, NF	USP/NF	
HCl 0.1 M	USP/NF	
Purified water, USP	USP/NF	

Table 2 Concentration of Components in Oxybutynin Gel 3.00 %

Ingredient	Oxybutynin Gel Concentration (% w/w)	Oxybutynin Gel Concentration (mg/g)	Maximum value from IIG for topical or transdermal
Oxybutynin	3.00	30.0	N/A
Diethylene glycol monoethyl ether, NF (DGME) ¹ (b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)			
Hydroxypropyl cellulose, NF			
Propylene glycol, USP			
Butylated hydroxytoluene, NF			
HCl 0.1 M			
Purified water, USP			

(b) (4)

It should be noted that the formulation of oxybutynin 3% gel used in initial clinical trials was found to contain traces of (b) (4). This impurity can be (b) (4) suspected to be potential carcinogenic and genotoxic in animal studies. Therefore, the Applicant changed the formulation (b) (4)

(b) (4)

(b) (4) Therefore, the Applicant evaluated

the effect of this change in *ex vivo* skin penetration studies using both pig and human skin (Study AP-1034) (Figures 1 and 2).

Figure 1 Ex Vivo Transdermal Oxybutynin Cumulative Delivery from 3% Gel Formulations in Pig Skin

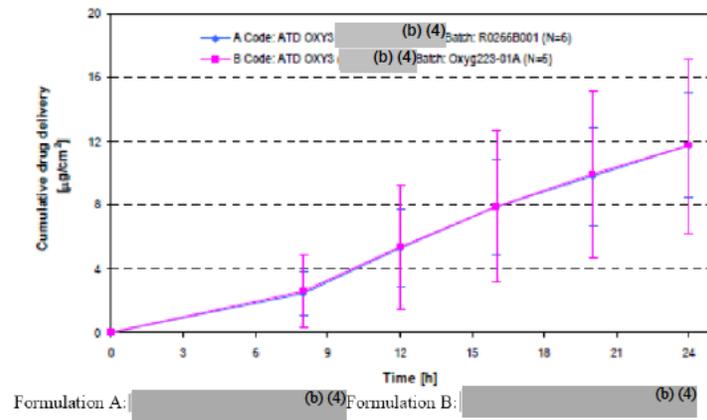
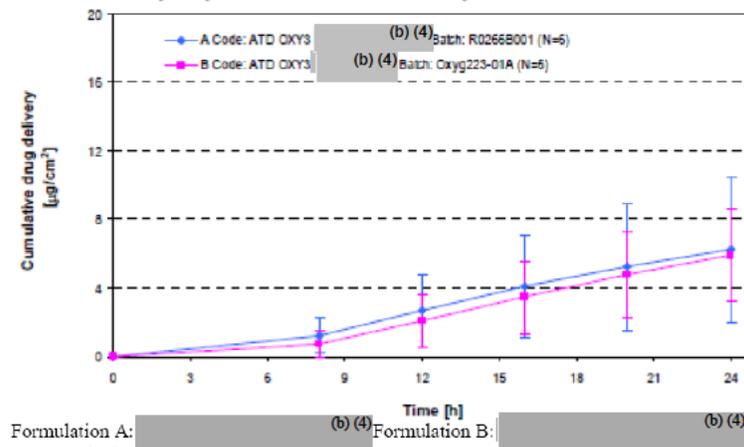


Figure 2 Ex Vivo Transdermal Oxybutynin Cumulative Delivery from 3% Gel Formulations in Human Skin



The results of this study indicated that the formulation change had no significant effect on skin penetration. However, as these *ex-vivo* studies do not have much regulatory utility besides getting some idea about penetration behaviors of the formulations, a comparative bioavailability study (Study SCO 5432) comparing the old (Reference) and new (Test) formulations was conducted. The results demonstrated that the two formulations are not bioequivalent. Since the exposure after the new formulation (b) (4) (Treatment A) is higher than that of the old formulation (b) (4) (treatment B) and the drug is relatively safe at the proposed dose of 84 mg, the inclusion of the 130 patients from the Phase III study who have been treated with the old formulation is acceptable from the clinical pharmacology perspective.

The reason for the inclusion of the 130 patients in the analysis of the data is to improve the statistical power of the trial to establish the efficacy of the treatment with the new oxybutynin gel. Therefore, though the two formulations are not bioequivalent, from the clinical pharmacology perspective an adequate link was established between the old

formulation (b) (4) and the new formulation (b) (4) This conclusion was communicated to the Applicant on November 2, 2009 (see *Clinical Pharmacology review*).

Reviewer's Comments: Based on the above *Clinical Pharmacology* recommendation, which was communicated to the sponsor on November 2, 2009, regarding linking / bridging the two formulations, the Applicant was not asked to conduct any other bridging study (e.g., *in vitro* release testing).

As part of the drug product specification, the sponsor proposed "Diffusion Rate" as a specification parameter. This Biopharmaceutics review will focus on the method and proposed acceptance criteria for this specification.

Diffusion Rate Determination (Method (b) (4))

Method (b) (4) was used for evaluation of the diffusion rate of Oxybutynin Gel 3.0%, drug product. (b) (4)

(b) (4). The following table summarizes the optimized diffusion method parameters:

(b) (4)

Using the above method, the Applicant proposes the "Diffusion Rate" specifications for finished products as described below:

(b) (4)

While the Agency acknowledges and accepts the analytical method (HPLC) validation report (b) (4) dated 05/21/2008, during the review of the above method, the

reviewer had several questions, which were sent to the Applicant in an Information Request (IR) Letter on 7/15/2011, The questions were as follow:

Please submit full development report of the diffusion method (b) (4) The report should specifically describe justification (s) for each of the following:



The applicant responded to the IR in their correspondence dated July 22, 2011 (SN0008). The submitted document QUC-11-002 entitled “AnturoI Diffusion Rate (Release rate) Development Report” dated July 21, 2011. In this report, they provided their justification of different parameters being used in the diffusion rate/release rate calculations. During the review of the report, the following issues were identified and another IR Letter has been drafted and will be sent out to the Applicant. .

1. Please submit raw data (in electronic format) from each cell at each time point used to calculate slope (diffusion rate) for each formulation at different time in the stability protocol.
2. Clearly indicate the method and associated data used to calculate slope and RSD values used in Table 1 and Table 2 in the Statistical Specifications Calculation. Also, clarify how and why are you intending to use the “Diffusion Rate: RSD” as part of your release and stability specifications. Please note that the same specification should be used for both release and stability
3. Explain how you came up with a “*a priori*” acceptance criteria for slope and RSD values.
4. As proposed, (b) (4)
That is not what the Agency agrees upon. We recommend that you calculate the ranges based on Mean \pm 90% CI (confidence interval) data.
5. Please designate the “Slope” values as “Release Rate” in your product specifications.
6. Please explain why the value of slope (b) (4) for the batch “HKC” as submitted in the original submission is different (b) (4) in the amendment submitted on 8/5/11 in Table 41.

7. In your stability report – 2011-001 Ver. 00 signed on 8/2/11, on Page 65 under section 7.9, you quoted “*There are, however, obvious inter-batch differences. The batch pairs HKB/KHV and HKC/KHW have diffusion rates that are significantly different*” ^{(b) (4)}
- ” Please explain what *in-vivo* data you have to assure that product batches with such different viscosities and diffusion rates will have similar *in-vivo* performance (e.g., bioavailability, efficacy and safety). Also, explain what steps you plan to take to control grades of ^{(b) (4)} to be used in your commercial product batches to have a tighter control of your product quality and performance.

Reviewer’s Comments:

1. *It is not clear, why the document QUC-11-002 entitled “Anturol Diffusion Rate (Release rate) Development Report” was created on July 21, 2011 after receiving the IR from the Agency dated July 15, 2011. It raises some concerns, please explain.*
2. *A full review of the justification of the different parameters used in the diffusion/release method development and the proposed specification can not be made without evaluating the answers from Applicant for the outstanding questions.*
3. *As this point, the application is considered incomplete from Biopharmaceutics point of view.*

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/s/

TAPASH K GHOSH
10/06/2011

ANGELICA DORANTES
10/06/2011