

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202513Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 02-Dec-2011
To: CMC Review #1 for NDA 202-513
From: Bogdan Kurtyka, Ph.D.
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Donna Christner, Ph.D.
Subject: **Final recommendation for NDA 202-513**

Previous CMC Review #1 dated 25-JUN-2010 noted following deficiencies with a recommendation of "Non Approval" action.

- A. This NDA has **not** provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.
1. *The adequacy of the acceptance criteria for the test of diffusion rate in the specification of the drug product has not been established yet. Therefore, the proposed specification of the drug product is not deemed to assure the quality of the drug product.*
 2. *The (b) (4) in the Container/closure system that will be used for future marketed product has been changed from the one currently described in the application, and whether or not this change will impact on the drug product has not been demonstrated.*
- B. In addition, labels do **not** have adequate information as required
3. Regarding the Package Insert:
- *"Highlights" section should list a correct established name as follows:
(oxybutynin) gel*
 - *"Dosage Forms and Strengths" section should list a description of the identifying characteristics.*
 - *"Description" section should have proprietary name, established name, dosage form, and route of administration.*
 - *"How Supplied/Storage and Handling" section should list the strength of dosage form.*
4. Regarding the labels:
- *According to 21CFR 201.51 declaration of net quantity for semi-solid drug products should be expressed in terms of weight instead of volume on the container and carton labels.*
 - *Also the container and carton label should be revised as follows:
Anturol
(oxybutynine) gel 3%*
 - *All inactive ingredients should be described in the carton label per 21CFR 201.100(b)(5)*

The sponsor addressed above issues satisfactorily in the submissions dated 07-Oct-2011, 09-Nov-2011, and 01-Dec-2011.

Recommendation and Conclusion

Therefore, from the ONDQA perspective, this NDA is now recommended for “Approval”.

Review Notes

Deficiency 1.

Biopharm review addressing this issue was checked into DARRTS on 08-Nov-2011. The sponsor was asked to change the diffusion rate attribute name to release rate. Also, based on the new submitted data the Agency proposed interim release rate acceptance criteria of (b) (4) for batch release and stability. The sponsor accepted both recommendations and on 09-Nov-2011 submitted the supplement with the updated specification.

The sponsor also committed to collect and submit additional in vitro drug release rate data from at least ten commercial batches of drug product. These data will be used to set the final regulatory acceptance criteria for the release rate test. 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 will be submitted to the Agency.

Evaluation:

After reviewing all submitted information Biopharm reviewer recommended "Approval" action from the Biopharmaceutics perspective for NDA 202-513 in the review addendum checked in to DARRTS on 15-NOV-2011. The addendum also states that no formal Post Marketing Commitment for re-assessment of release rate acceptance criteria is needed.

The CMC reviewer also confirmed that new acceptance criteria for release rate do not change the conclusion of assessment of stability data. This deficiency is ADEQUATELY addressed and no formal Post Marketing Commitment is necessary.

Deficiency 2.

In the amendment dated 07-Oct-2011 the sponsor submitted information on the new container closure system as follows:

- The materials of construction for the new components remain unchanged from the former components; therefore all product contact surfaces also remain unchanged.

- Since no changes to product contact surfaces have been affected with this change, all container closure studies conducted by Antares Pharma remain pertinent for this application and no further qualification work is required.
- Drug product samples prepared using new components from first three commercial lots and one lot annually thereafter will be monitored for stability.

Evaluation: The submitted information is ADEQUATE and successfully resolves this issue.

Deficiency 3.

In the amendment dated 01-Dec-2011 the sponsor submitted an updated package insert with the following corrections:

- "Highlights" section list the correct established name as follows:
(oxybutynin) gel

- “Dosage Forms and Strengths” section lists a description of the identifying characteristics as “ANTUROL is a homogeneous, colorless to slightly colored gel 3%.”
- “Description” section lists proprietary name, established name, dosage form, and route of administration.
- “How Supplied/Storage and Handling” section lists the strength of dosage form as 3%.

Evaluation: The submitted information is ADEQUATE and successfully resolves this issue.

Deficiency 4.

In the amendment dated 01-Dec-2011 the sponsor submitted an updated labeling with the following corrections:

- Declaration of net quantity is expressed in terms of weight (instead of volume) in compliance with 21CFR 201.51.
- Also the container and carton labels were revised as follows:
Anturol
(oxybutynine) gel 3%
- All inactive ingredients are listed in the carton label in compliance with 21CFR 201.100(b)(5).

Updated container and carton labels for 92 containers are presented below. Container and carton labels for 42 g presentation include the same information.

(b) (4)



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

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/s/

BOGDAN KURTYKA
12/02/2011

MOO JHONG RHEE
12/02/2011
Chief, Branch IV

NDA 202-513

**ANTUROL (oxybutynin) gel
3%**

Antares Pharma Inc.

Bogdan Kurtyka, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division II, Branch IV**

**CMC REVIEW OF NDA 202-513
For the Division of Reproductive and Urologic Products (HFD-580)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 202-513

2. REVIEW #: 1

3. REVIEW DATE: 07-OCT-2011

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	20-DEC-2010
Amendment – Stability update	06-MAY-2011
Amendment – Responses to IR	29-JUL-2011
Amendment – Stability update	05-AUG-2011

7. NAME & ADDRESS OF SPONSOR:

Name: Antares Pharma, Inc.
Address: 250 Phillips Blvd., Suite 290
Ewing, NJ 08618
Representative: Dave J. Kaushik, Sr. VP Product Development
Telephone: 609-359-3020

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Anturol
b) Non-Proprietary Name: (USAN) Oxybutynin
c) Code Name/# (ONDQA only): None
d) Chem. Type/Submission Priority (ONDQA only):
• Chem. Type: 3
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

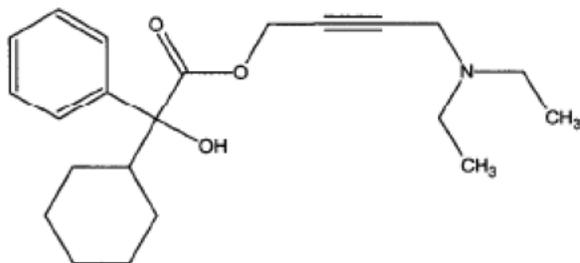
10. PHARMACOL. CATEGORY: An antimuscarinic agent indicated for the treatment of overactive bladder.

CMC Review Data Sheet

11. DOSAGE FORM: Gel CODE: 066
12. STRENGTH/POTENCY: 3%
13. ROUTE OF ADMINISTRATION: Transdermal CODE: 358
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: Benzene acetic acid, α -cyclohexyl- α -hydroxy-4-(diethylamino)-2-butynyl ester
 USAN Name: Oxybutynin
 CAS Number: 5633-20-5
 Structural Formula: _____



Molecular Formula: $C_{12}H_{31}NO_3$
 Molecular Weight: 357 **1**

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Oxybutynin base	3	Adequate	09-DEC-2010	
	III	(b) (4)		4	N/A	N/A	

CMC Review Data Sheet

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	06-APR-2011	Bogdan Kurtyka
Pharm/Tox	Cytotoxicity study 686647 acceptable for (b) (4) components	22-SEP-2011	Laurie McLeod-Flynn
Biopharm	Diffusion rate method and its validation acceptable. Acceptance criterion for the diffusion rate is not acceptable	06-OCT-2011	Tapash Ghosh
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	Proprietary name acceptable	26-JUL-2011	Walter Fava
EA	Categorical exclusion granted (see review)	22-JUN-2011	Bogdan Kurtyka
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 202-513

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has *not* provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product.

All facilities involved are in compliance with cGMP.

In addition, labels do *not* have adequate information as required.

Therefore, from a CMC perspective, this NDA is *not* recommended for approval in its present form until the issues listed in the “List of Deficiencies” are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The sponsor references DMF [REDACTED] (b) (4) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of oxybutynin. A letter of authorization to cross reference the DMF is provided in the application.

DMF [REDACTED] (b) (4) has been reviewed on 09-DEC-2010 in support of [REDACTED] (b) (4) for [REDACTED] (b) (4) and found ADEQUATE. Because drug product proposed in the application under review is a topical gel, the referenced DMF is deemed adequate to support this NDA.

(2) Drug Product

The drug product is a transparent, colorless to slightly yellow, non-occlusive gel containing 3.0% w/w of oxybutynin. The sponsor used a proprietary Advanced Transdermal Delivery (ATD) gel technology to develop the desired formulation. The ATD technology is based on the use of a specific combination of permeation enhancers to achieve sustained transdermal drug delivery. [REDACTED] (b) (4)

Executive Summary Section

(b) (4)

The drug product specification includes identification, assay, and content uniformity of the active ingredient, assays of functional excipients ((b) (4)), diffusion rate, impurities, pH, viscosity, color, minimum fill, and microbial purity tests. All analytical methods were found acceptable for assuring the identity, strength, purity, and quality, except the test for the diffusion rate of which acceptance criteria are not deemed satisfactory (see the Biopharm's Review by Dr. Tapash Ghosh dated 06-Oct-2011).

The container/closure system for the oxybutynin gel consists of a (b) (4) /aluminum foil (b) (4) (b) (4) which contains drug product. The (b) (4) is secured inside a polypropylene bottle which does not make product contact. A metered pump is used to dispense the oxybutynin gel. A polypropylene cap closure covers each filled container. However, the information described in the referenced DMF indicates that (b) (4) in the container/closure system that will be used for future marketed product is physically modified from the one currently described in the application. Although the cytotoxicity data of the extractables from the original (b) (4) are deemed acceptable per Pharm/tox review dated 22-Sep-2011, it is not certain whether the new (b) (4) is also acceptable for preserving the purity and quality of the drug product.

The sponsor provided the results of 18 months long-term stability studies and proposed a 24-month expiration dating period under the controlled room conditions. The provided stability data support the proposed expiration dating period.

B. Description of How the Drug Product is Intended to be Used

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

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

B. Basis for Not-Approval Recommendation

1. 21CFR 314.125(b)(1)

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

2. 21CFR314.125(b)(6)

- Labels/labeling do not have required information (See the List of Deficiencies on

Executive Summary Section

P.53).

Therefore, from a CMC perspective, this NDA is *not* recommended for approval at this time.

III. Administrative

- A. Reviewer's Signature:** *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA
- B. Endorsement Block:** *(See appended electronic signature page)*

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV/Division II/ONDQA
- C. CC Block:** Entered electronically in DARRTS

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/s/

BOGDAN KURTYKA
10/07/2011

MOO JHONG RHEE
10/07/2011
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division: Division of Reproductive and Urologic Products
NDA: 202513
Applicant: Antares Pharma, Inc
Stamp Date: 08-Feb-2011
PDUFA Date: 08-Dec-2011
Trademark: Anutrol
Established Name: Oxybutynin
Dosage Form: Gel, 3%
Route of Administration: Transdermal
Indication: Over active bladder

CMC Lead: Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	X	<input type="checkbox"/>
Comments for 74-Day Letter	X	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

ANTUROL™ (Oxybutynin Gel 3%) is a transparent, fast-drying, colorless to slightly yellow, non-occlusive gel containing 3.0% w/w oxybutynin free base. The oxybutynin drug product is a homogeneous gel, without particles.

The container/closure system for the oxybutynin gel, 3.0% consists of a (b) (4) /aluminum foil/ (b) (4) (b) (4) (b) (4) which contains the product. The (b) (4) is secured inside a polypropylene bottle which does not make product contact. The product will be packaged in 100 (b) (4) bottle configurations, with target fills of 100 mL and 45 mL, respectively. The (b) (4) 45mL fill size will be packaged in two presentations. A single bottle will be packaged, labeled and cartoned as a sample presentation, and a package presentation of two (b) (4) 45 mL containers in one larger carton will be a commercial product.

A metered pump, (b) (4) is used to dispense the oxybutynin gel. A polypropylene cap closure is also applied to each filled container.

B. Critical issues for review

The sponsor has deleted the following tests on stability: (b) (4)

The sponsor will submit additional stability data prior to month 6 of the review cycle as agreed to by the FDA in a letter dated 30-Sep-2010.

The name is presented in many different formats. The correct form would be Anutrol (oxybutynin gel) 3%. This information will need to be standardized, but this can be addressed at a later time in the review cycle.

C. Comments for 74-Day Letter

Submit color mock-ups of all carton/container labels to allow full review and update all labeling with the appropriate NDC numbers.

D. Recommendation:

This NDA is fileable from a CMC perspective. Bogdan Kurtyka, Ph.D. has been assigned as the primary CMC reviewer. Dr. Tapah Ghosh is the assigned BioPharmaceutics reviewer. Since one oxybutynin gel has been approved, this NDA is recommended for a Branch level Regulatory Briefing.

Donna F. Christner, Ph.D.

NDA Number: 202513 Type: 5

Established/Proper Name:
Anutrol (oxybutynin) gel

Applicant: Antares Letter Date: 08-Feb-2011

Stamp Date: 08-Feb-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		356h
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.		X	N/A

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		356 h
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		356h

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		356h
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion as per 21 CFR 25.31(a)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference DMF (b) (4)
15.	Does the section contain controls for the DS?	X		Cross-reference DMF (b) (4)
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	Not a filing issue
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	Not a filing issue

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		24 months of expiry requested based on three registration lots manufactured at the intended commercial site (b) (4) and two stability batches manufactured at pilot scale at Antares
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	Not a filing issue
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	Not a filing issue

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		X	Not a sterile product

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Oxybutynin base	17-Jun-2010	Adequate on 08-Dec-2010 by R. Powers
	IV	(b) (4)	(b) (4)	13-Jul-2010	No review found. Normally not needed for excipients
	IV	(b) (4)	(b) (4)	22-Jun-2010	No review found. Normally not needed for excipients
	III	(b) (4)	(b) (4)	17-Jun-2010	No review found. May required review unless adequate information is provided in the NDA
					See ONDC Policies on Bottles and Blisters*

*Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
 Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		SPL label provided
33.	Have the immediate container and carton labels been provided?	X		Labels provided as black lettering on white background. Sponsor should be advised to submit color mock-ups to allow review. The NDC number should be updated on all labels.

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?			Describe potential review issues here or on additional sheets

{See appended electronic signature page}

Donna F. Christner, Ph.D.
 CMC Lead
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
 Chief, Branch IV
 Division of New Drug Quality Assessment II
 Office of New Drug Quality Assessment

Date

REVIEW NOTES

Clinical studies in support of this NDA were performed under IND 70,527. The reviewer should access DARRTS to learn the full regulatory history of this application.

Of note, the FDA agreed in a letter dated 30-Sep-2010 that the sponsor could supplement the NDA with additional stability data prior to month 6 of the review cycle.

(b) (4) During the initial phases of the Phase 3 trials, a (b) (4) impurity was found in the (b) (4) formulation. (b) (4)

Table 2.3.P.2 -2 Descriptions and Compositions of Oxybutynin Gel, 3.0% (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)			
Hydroxypropyl cellulose			

Component and Grade	Phase 3 Concentration Modified Formulation (%w/w)	Pre Phase 3 Concentration Original Formulation (%w/w)	Function
(b) (4)			(b) (4)
Propylene glycol, USP	(b) (4)		
(b) (4)			
Butylated hydroxytoluene, NF			
HCl 0.1 M (b) (4)			
(b) (4)			
Purified water, USP			(b) (4)

This change in formulation was bridged by in vitro permeability studies conducted with pig and human skin, in vitro release data to support both the formulation and manufacturing site change, and a bioequivalence study comparing the two formulations.

The formulations used for each study are outlined below:

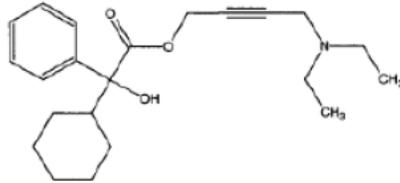
Table 2.3.P.2-3 Pre-clinical and Clinical Study Material, Batch Number and Intended Use

Batch	Manufacturer	(b) (4)	Used in clinical trial
031101	(b) (4)		Phase I
Oxyg146-03B/P1	Antares		Phase II
C0900A001	(b) (4)		Application site study
C0847B001			Phase III
Oxyg146-20B/P1	Antares		BE Study
Oxyg223-05B/P1	Antares		
R0266B003	(b) (4)		Phase III
HKB			Phase III Labeling studies (sunscreen, showering, transfer)

DRUG SUBSTANCE

The drug substance is oxybutynin. The majority of the information is in the cross-referenced DMF which was recently reviewed in December 2010 and found to be ACCEPTABLE. The following information is provided in the NDA.

Structural Formula:



Molecular Formula: C₂₂H₃₁NO₃

Relative Molecular Mass: 357 (b) (4)

The following site is responsible for the manufacture of the drug substance:

Manufacturing Facilities: Manufacture, release and stability testing of active pharmaceutical ingredient



Comment: EES was submitted on 25-Feb-2011 by Rebecca McKnight. (b) (4) facility is acceptable to OC as of that date.

1 page has been withheld in full as B(4) CCI/TS immediately following this page

DRUG PRODUCT

The sponsor states the following:

ANTUROL™ (conditionally approved trade name synonymous with Oxybutynin Gel 3%) is a transparent, fast-drying, colorless to slightly yellow, non-occlusive gel containing 3.0% w/w oxybutynin free base. The oxybutynin drug product is a homogeneous gel, without particles.

The container/closure system for the oxybutynin gel, 3.0% consists of a (b) (4) /aluminum foil/ (b) (4) (b) (4) (b) (4) which contains the product. The (b) (4) is secured inside a polypropylene bottle which does not make product contact. The product will be packaged in 100 (b) (4) mL bottle configurations, with target fills of 100 mL and 45 mL, respectively. The (b) (4) /45mL fill size will be packaged in two presentations. A single bottle will be packaged, labeled and cartoned as a sample presentation, and a package presentation of two (b) (4) /45 mL containers in one larger carton will be a commercial product.

A metered pump, (b) (4) is used to dispense the oxybutynin gel. A polypropylene cap closure is also applied to each filled container.

The formulation is as follows:

Table 2.3.P.1-2 Concentration of Components in Oxybutynin Gel 3.0%, and Maximum Levels Listed in IIG

Ingredient	Oxybutynin Gel Concentration (% w/w)	Oxybutynin Gel Concentration (mg/g)	Maximum value from IIG for topical or transdermal
Oxybutynin	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)

All excipients are compendial and controlled using compendial methods. The sponsor has provided information in the table above on the levels of the excipients used in FDA-approved products.

The sponsor has identified the roles of each excipient in the table below:

Table 2.3.P.1-1 Components of Oxybutynin 3.0% Drug Product

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

The sponsor states that they developed this gel using a unique and proprietary advanced transdermal gel technology (ATD™) that facilitates skin permeation. (b) (4)

(b) (4) They have included assay tests for these components in the specifications.

Comment: Information is adequate to allow review.

Manufacturers:

The following facilities have responsibility for the manufacture of the drug product:

(b) (4)

Comment: EES was submitted on 25-Feb-2011 by Rebecca McKnight. The (b) (4) was scheduled for inspection and the (b) (4) is acceptable to OC as of that date.

The sponsor has provided the following manufacturing flow chart. A narrative is also provided.

(b) (4)



Comment: Information is adequate to allow review.

2 pages have been withheld in full as B(4) CCI/TS immediately following this page

Comment: The sponsor has deleted the following tests on stability: (b) (4)

CONTAINER CLOSURE

The sponsor has provided the following information on the container closure system:

The container/closure system for the oxybutynin gel, 3.0% consists of a (b) (4) /aluminum foil/ (b) (4) (b) (4) (b) (4) which contains the product. The (b) (4) is secured inside a polypropylene bottle which does not make product contact. The product will be packaged in 100 (b) (4) bottle configurations, with target fills of 100 mL and 45 mL, respectively. The (b) (4) /45mL fill size will be packaged in two presentations. A single bottle will be packaged, labeled and cartoned as a sample presentation, and a package presentation of two (b) (4) /45 mL containers in one larger carton will be a commercial product.

A metered pump, (b) (4) is used to dispense the oxybutynin gel. A polypropylene cap closure is also applied to each filled container. The product contact components were tested for suitability of use.

The sponsor outlines a number of compatibility studies that were performed on the container closure system. These should be adequate to support the use of the container closure system.

Comment: The DMF may require review if adequate information is not provided in the NDA.

STABILITY

The sponsor has provided the following stability package in support of their requested 24 month expiry:

Stability data for the registration batches stored in the upright, horizontal, and inverted positions in the (b) (4) multiple dose (b) (4) package presentation are provided for stability storage times of:

- 6 months at 40°C/75%RH (3 batches)
- 9 months at 25°C/60%RH (2 batches), and 18 months at 25°C/60%RH (1 batch)

Stability data for the registration batches stored in the upright, horizontal, and inverted positions in the (b) (4) multiple dose (b) (4) package presentation are provided for stability storage times of:

- 6 months at 40°C/75%RH (2 batches)
- 9 months at 25°C/60%RH (2 batches)

Stability data for the supportive batches stored in the upright position, and in the (b) (4) (b) (4) package presentation, are provided for stability storage times of:

- 6 months at 40°C/75%RH (2 batches)
- 12 months at 30°C/65%RH (2 batches)
- 19 months at 25°C/60%RH (1 batch), 20 months at 25°C/60%RH (1 batch)

Comment: Adequate stability is provided in order to set an expiry. It is a review issue on whether the package will support the requested 24 months. The sponsor will submit additional stability data prior to month 6 of the review cycle as agreed to by the FDA in a letter dated 30-Sep-2010.

LABELING

The sponsor has provided a Physician's Insert which includes the SPL labeling. The carton/container labels are provided as black lettering on white background. Sponsor should be advised to submit color mock-ups to allow review. The NDC number should be updated on all labels.

The name is presented in many different formats:



Anutrol (oxybutynin gel) 3%

The correct form would be Anutrol (oxybutynin gel) 3%. This information will need to be standardized, but this can be addressed at a later time in the review cycle.

Comment: The sponsor should submit color mock-ups of all carton/container labels to allow full review and update all labeling with the appropriate NDC numbers.

The name is presented in many different formats. The correct form would be Anutrol (oxybutynin gel) 3%. This information will need to be standardized, but this can be addressed at a later time in the review cycle.

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

/s/

DONNA F CHRISTNER
04/04/2011

MOO JHONG RHEE
04/04/2011
Chief, Branch IV