

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202513Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202513/Original 1

SUPPL #

HFD #

Trade Name ANTUROL

Generic Name oxybutynin gel, 3%, 84 mg

Applicant Name Antares Pharma, Inc.

Approval Date, If Known December 7, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?
YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?
YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21351	Oxytrol (oxybutynin), 3.9 mg/24 hrs transdermal system
NDA# 22204	Gelnique (oxybutynin chloride), gel, 10 %
NDA# 20897	Diropan XL (oxybutynin chloride), 5mg, 10 mg, and 15 mg extended release tablets
NDA# 17577	Ditropan (oxybutynin chloride), 5mg tablets

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# Same as Part II, #1, because this is not a combination product

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2)

there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 20070060 A Double-Blind, Randomized, Parallel, Placebo-Controlled, Multicenter Study Evaluating the Effect of Treatment with Topically Administered Oxybutynin Gel in Patients with Urinary Frequency and Urge and Mixed Urinary Incontinence with a Predominance of Urge Incontinence Episodes with an Open-Label Extension

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 20070060 A Double-Blind, Randomized, Parallel, Placebo-Controlled, Multicenter Study Evaluating the Effect of Treatment with Topically Administered Oxybutynin Gel in Patients with Urinary Frequency and Urge and Mixed Urinary Incontinence with a Predominance of Urge Incontinence Episodes with an Open-Label Extension

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean

providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 070527 YES ! NO
! Explain:

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Nenita Crisostomo, R.N.
Title: Regulatory Health Project Manager
Date: December 2, 2011

Name of Office/Division Director signing form: Audrey Gassman, M.D.
Title: Deputy Director, Acting - Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

NENITA I CRISOSTOMO
12/06/2011

AUDREY L GASSMAN
12/07/2011

Crisostomo, Nenita

From: Greeley, George
Sent: Friday, November 04, 2011 12:45 PM
To: Crisostomo, Nenita
CC: Mathis, Lisa; Addy, Rosemary; Suggs, Courtney; Lee, Catherine S.; Monroe, Scott
Subject: NDA 202-5133 Anturol

Importance: High

Attachments: 1_Pediatric_Record.pdf

Hi Nita,

This email serves as confirmation of the review for Anturol (Oxybutynin 3%) conducted by the PeRC PREA Subcommittee on November 2, 2011.

The Division presented a full waiver in pediatric patients for the indication of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency because the product does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients.

The PeRC agreed with the Division to grant a full waiver for this product because the product would be unsafe.

The amended pediatric record is attached for Anturol.



_Pediatric_Record
.pdf (68 KB)...

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
FDA/CDER/OND
10903 New Hampshire Avenue
Bldg. 22, Room 6467
Silver Spring, MD 20993-0002
Phone: 301.796.4025
Email: george.greeley@fda.hhs.gov

 Please consider the environment before printing this e-mail.

1.3.3 Debarment Certification

Debarment statements are provided for Antares (Applicant), [REDACTED] (b) (4) [REDACTED] (b) (4)
[REDACTED] (b) (4)

Antares Pharma, Inc. Debarment Statement

[REDACTED] (b) (4)

[REDACTED] (b) (4)

1.3.3 Debarment Certification

Antares Pharma, Inc, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Pursuant to Section 306(k) of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Drug Enforcement Act of 1992, Antares Pharma, Inc, hereby certifies that we did not and will not use, in any capacity, the services of any person debarred under subsection (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this NDA.

Antares Pharma, Inc. certifies further that, during the previous five years, it has not sustained a conviction that is described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992. In addition, Antares Pharma, Inc, certifies that no person affiliated with the company that was responsible for the development or submission of this application has been convicted of an offense described in subsections (a) or (b) of the Generic Drug Enforcement Act of 1992.



Kaushik J. Dave RPh, PhD, MBA
Senior Vice President Product Development

16-NOV-2010

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202513/ Original 1	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Anturool Established/Proper Name: oxybutynin gel, 3% , 84 mg Dosage Form: metered gel		Applicant: Antares Pharma, Inc. Agent for Applicant (if applicable):
RPM: Nenita Crisostomo, R.N.		Division: Division of Reproductive and Urologic Products
<p>NDA: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): NDA 17577 Ditropan (oxybutynin chloride), 5mg tablets</p> <p>Provide a brief explanation of how this product is different from the listed drug. different form---a gel.</p> <p>If no listed drug, explain. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>December 8, 2011</u> 	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 	<input checked="" type="checkbox"/> None	
<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received	

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval, December 7, 2011
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Submitted December 1, 2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	May 4, 2011 December 20, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Submitted December 1, 2011, Division-proposed
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	May 4, 2011 December 20, 2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	December 1, 2011
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	July 29, 2011 July 26, 2011 December 6, 2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> DDMAC(OPDP) 11/2/11 <input checked="" type="checkbox"/> RPM 4/7/11 <input checked="" type="checkbox"/> DMEPA 10/21/11 <input checked="" type="checkbox"/> DRISK(DMPP) 11/2/11 <input checked="" type="checkbox"/> SEALD 6/28/11, 12/1/11 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	5/3/11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) 12/1/11
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) 12/7/11
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	11/2/11 <input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg May 2, 2006
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
• Preliminary Comments for Type C Mtg	October 22, 2009
• Teleconference w/ Antares: 505b2	March 30, 2011
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 7, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None December 6, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical review(s) (<i>indicate date for each review</i>)	December 6, 2011 April 4, 2011, Filing
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review, page 17-18., December 6, 2011
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None November 30, 2011 April 4, 2011, Filing
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	December 5, 2011, addendum October 13, 2011 April 7, 2011, Filing
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	September 22, 2011 April 20, 2011, Filing
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None, see P/T review, 9/22/11, page 3-4
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product Quality review: ONDQA CMC	April 4, 2011, Filing October 7, 2011 December 2, 2011
• Product quality review: ONDQA biopharmaceutics	October 6, 2011 November 8, 2011 November 15, 2011, addendum
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review, 10/7/11, page 53
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: April 6, 2011 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

/s/

NENITA I CRISOSTOMO
12/07/2011

Crisostomo, Nenita

To: 'Kaushik Dave'
Cc: 'Gerald Orehostky'
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Hi Kaushik,

This is acceptable. With our minor formatting edits, please accept the changes and we shall consider this a final version. I will attach this copy to the Action letter and you can prepare to submit officially, along with the other final versions of the labeling as we have previously agreed-upon, to the EDR.

Thank you so much for your and your Team's hard work in this project. We hope to take action on December 7, 2011, a day earlier than it is due, if all goes just as well.

Have a great day!
nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Wednesday, November 30, 2011 3:10 PM
To: Crisostomo, Nenita
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Attached is the version of PI with the PPI. Please confirm this is acceptable and final.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020


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Thank you.

12/6/2011

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, November 30, 2011 2:15 PM
To: Kaushik Dave
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Hi Kaushik,

Here is the label. All edits are inserted after reviewed by SEALD, mostly formatting. There is one item that they added and the Division agree: under Pediatrics sections of the Highlights and 8.4: they added **safety and** effectiveness..... Also, please insert the final-agreed-upon PPI onto this label after section 17, before 17.1. Please email the completed clean PI to me one more time as soon as possible today. Thank you so much for the hard work and patience.

Much appreciated,
nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Wednesday, November 30, 2011 12:44 PM
To: Crisostomo, Nenita
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Nita,
Attached is the clean version of the FINAL PI which was received from you on November 29, 2011 at 5:07PM.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020

(b) (6)

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Thank you.

12/6/2011

Reference ID: 3058478

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, November 30, 2011 12:37 PM
To: Kaushik Dave
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Great! Could you please email to me now a clean version of the PI that you will be submitting as a copy of the agreed-upon label?

Thank you,
nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Wednesday, November 30, 2011 12:30 PM
To: Crisostomo, Nenita
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Nita,
We have agreed on ALL labeling. We plan to submitted the same by the end of this week to the NDA.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, November 30, 2011 12:22 PM

12/6/2011

Reference ID: 3058478

To: Kaushik Dave
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Hi Kaushik,

I am following to see if we have an agreed-upon label based on my last email (below) yesterday? Please let me know as soon as possible.

Thank you so much,
nita

From: Crisostomo, Nenita
Sent: Tuesday, November 29, 2011 5:07 PM
To: 'Kaushik Dave'
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Hi Kaushik,

We accept your re-wording of section 14. In addition, we have some formatting changes. No other content changes.

Thanks,
nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Tuesday, November 29, 2011 4:25 PM
To: Crisostomo, Nenita
Cc: Gerald Orehostky
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Nita,

We have accepted all the agencies changes from the version emailed to Antares this afternoon (2:53 PM Nov 29, 2011). However, Antares proposes a final rewording in Section 14. Please let us know as soon as possible if this is acceptable then this will be the final version except for any formatting changes you may have.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618

12/6/2011

Phone: 609 359 3020

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Tuesday, November 29, 2011 2:53 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: RE: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation
Sensitivity: Confidential

Hi Jerry,

Attached is the Division's final version of the labeling. We have accepted all of your edits except for one item: under CLINICAL STUDIES section: we changed (b) (4) to 202 patients received placebo---please see our comments.

Also, under OVERDOSAGE section, we re-inserted the last sentence, If overexposure occurs, monitor patients until symptoms resolve[nc1] , which was inadvertently removed during the previous editing versions.

We have no further comments to the 92g container & carton labels, 42g sample carton/container (primary & twin-pack)

Please email to me your response on/before 10:00 am tomorrow, November 30, 2011. If you have any questions, please feel free to contact me.

Thanks,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

Hi Nita,

As indicated earlier, please find attached the the ANTUROL PI which includes the Agency's proposed changes that have been adopted and any changes suggested by Antares are highlighted in MS Word's Track changes

12/6/2011

Reference ID: 3058478

feature. Also, there are a few areas where Antares would appreciate clarification and/or confirmation from the Agency. These are noted in the Comments "bubbles".

Based on my records, you have indicated that the last versions of the following label components have been deemed final and are suitable for final submission, thus far:

- PPI
- 42g Twin-pack Carton

This leaves the following label components that require final agreement from the Agency:

- 92g Primary Container Label
- 92g Carton
- 42g Sample Only Primary Container Label
- 42g Sample Only Carton
- 42g Twin-pack Primary Container Label
- PI

Could you please confirm if my records are correct regarding the status of the various ANTUROL label components?

Should you have any questions, please feel free to contact Dr. Dave or myself. I will be away from the office for the next several days but if you cannot reach Dr. Dave, please feel free to contact me using my mobile number (b) (6) or via email as I will be checking in periodically.

Have a nice evening.

Best Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033

(b) (6)

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Thank you.

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Monday, November 28, 2011 3:53 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave

12/6/2011

Reference ID: 3058478

Subject: NDA 202-513: ANTUROL PI Including Proposed Changes and Requests for Clarification/Confirmation

Sensitivity: Confidential

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

12/6/2011

Reference ID: 3058478

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 21, 2011 3:53 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202-513: FDA-Proposed PI
Sensitivity: Confidential
Attachments: PI.to sponsor.11.21.11.doc

Hi Jerry,

Attached is our version of the Package Insert in response to your 11/15/11 version. Please respond with your version on or before November 28, 2011.

Thank you so much,
 nita

*Nenita Crisostomo, RN
 Regulatory Health Project Manager
 U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Division of Reproductive and Urologic Products
 Telephone: 301-796-0875
 Fax: 301-796-9897*

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Tuesday, November 15, 2011 4:50 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: NDA 202-513: Final Draft - Proposed PI
Sensitivity: Confidential

Dear Nita,

Per Dr. Dave's direction, I am forwarding for the Agency's review, a proposed draft version of the ANTUROL Package Insert (PI). I have included a final version in MS Word format that contains no marked sections. This file is identified with the suffix "CLEAN" in the filename. Alternatively, I have also provided this same version of the ANTUROL PI in MS Word format, however, this version exhibits the various changes made to the document originally provided to Antares from the Agency on 07 November 2011. This file is identified with the suffix "TRACKED CHANGES". In addition, a document is also attached to this email that summarizes the changes made within the PI. Please note that all changes proposed by the Agency have been addressed although the Agency's original comments were retained in the TRACKED CHANGES version for convenience when reviewing.

In some cases, Antares Pharma has included comments to address Agency feedback or request further clarification regarding proposed changes. (b) (4)

[Redacted]

12/6/2011

Reference ID: 3058478

(b) (4)

Should you have any questions or wish to discuss further any items noted above, please feel free to contact Dr. Dave or myself at any time.

Antares Pharma thanks you and the review team for the collaborative and interactive nature of the review process experienced thus far.

Best Regards

Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033 (b) (6)

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Thank you.

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

12/6/2011

Reference ID: 3058478

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 21, 2011 3:09 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturoi: PPI
Attachments: PPI.to sp 11.21.11.doc

Tracking:

Recipient	Read
'Gerald Orehostky'	
Kaushik Dave	
Kaul, Suresh	
Kwak, Jina	Read: 11/21/2011 3:11 PM
Hutchins, Shawna	
Townsend, Karen	

Hello Jerry,

We have accepted all of your changes and we have no further edits to the Patient Information. If you have no further edits to our version, as attached, please submit it officially to the electronic document room. You do not have to submit it in the SPL format yet. That can be done post-action.

However, if you have any further edits, please email your revised version to me asap today.

Thank you so much,
nita

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Thursday, November 17, 2011 4:59 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturoi: PPI

Hello Nita,

Per your earlier request, please find attached the completed PPI which includes all of the Agency's proposed changes accepted. A few minor corrections made by Antares can also be observed in this file using the Track Changes mode.

In addition, I have provided the Carton proofs that were updated per the Agency's recommendations which you provided via email on 16 November 2011 (see attached). Please note that changes proposed by the Agency were accepted. The remaining Primary Container Labels should be forthcoming shortly.

If possible, could you please provide an estimate of when we may receive the PI including the Agency's comments/changes?

Thank you. Should you have any questions, please feel free to contact Dr. Dave or myself at any time.

Kind Regards

12/6/2011

Reference ID: 3058478

Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033

(b) (6)

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, November 17, 2011 1:14 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturoi: PPI

My apologies. I am resending to include the PPI this time around.
Thanks,
nita

From: Crisostomo, Nenita
Sent: Thursday, November 17, 2011 1:12 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturoi: PPI

Hi Jerry,

Attached is our response to your 11/11/11 PPI. Please accept all of our changes and mark your changes (if any more) on a clean copy and email it to me on or before 12Noon on Monday, 11/21/11, complete with your justification of your proposed changes. If you have no further changes, please let me know as soon as possible.

Thank you so much,
nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

12/6/2011

Reference ID: 3058478

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Friday, November 11, 2011 3:19 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturo: carton/container labels

Dear Nita,

In response to the Agency's request, Antares Pharma has updated ANTUROL labeling components consistent with the Agency's recent recommendations.

Please find attached the amended labels for including three (3) Primary Container Labels, three (3) Cartons and the Patient Information Insert. Antares Pharma continues to work to finalizing the Package Insert which should be complete very soon. As soon as I obtain a more specific completion date, I will notify you immediately.

In addition to providing the attached labels, we would also appreciate clarification pertaining to the Agency's Biostatistical analysis of the Anturo Phase 3 clinical data which we did not have a chance to address during the Teleconference which was held on 09 November 2011. Could you please provide the p-values that the Agency's Biostatisticians generated for the primary and secondary endpoints for the ANTUROL (b) (4)

Thank you in advance for addressing Antares' request. Should you have any questions, please feel free to contact Dr. Dave or myself at any time.

Enjoy your long weekend.

Kind Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033
(b) (6)

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Monday, November 07, 2011 3:55 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturo: carton/container labels

12/6/2011

Reference ID: 3058478

Hi Jerry,

You are correct that oxybutynine is a typographical error. Please remove the "e" at the end. Thanks so much for bringing it to our attention.

Best Regards,
nita

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Sent: Monday, November 07, 2011 3:49 PM
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Hello Nita,

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Cc: Kaushik Dave
Subject: NDA 202513 Anturol: carton/container labels

Hi Jerry,

12/6/2011

Reference ID: 3058478

Request below is from our Chemistry reviewer regarding the carton/container labeling. The comments from Division of Medication Error Prevention and Analysis (DMEPA) will follow in a separate email. Please revise your carton/container labeling accordingly and email the mock labels to me on/before 12:00 P.M. on November 10, 2011.

- 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)

Thank you so much,
Nita
Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, November 17, 2011 1:12 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturoi: PPI

Tracking: **Recipient** **Read**
 'Gerald Orehostky'
 Kaushik Dave
 Kaul, Suresh Read: 11/17/2011 1:24 PM
 Hutchins, Shawna Read: 11/17/2011 1:15 PM
 Kwak, Jina Read: 11/17/2011 1:14 PM
 Jarow, Jonathan

Hi Jerry,

Attached is our response to your 11/11/11 PPI. Please accept all of our changes and mark your changes (if any more) on a clean copy and email it to me on or before 12Noon on Monday, 11/21/11, complete with your justification of your proposed changes. If you have no further changes, please let me know as soon as possible.

Thank you so much,
 nita

*Nenita Crisostomo, RN
 Regulatory Health Project Manager
 U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Division of Reproductive and Urologic Products
 Telephone: 301-796-0875
 Fax: 301-796-9897*

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12/6/2011

Reference ID: 3058478

In addition to providing the attached labels, we would also appreciate clarification pertaining to the Agency's Biostatistical analysis of the Anturool Phase 3 clinical data which we did not have a chance to address during the Teleconference which was held on 09 November 2011. Could you please provide the p-values that the Agency's Biostatisticians generated for the primary and secondary endpoints for the ANTUROOL (b) (4)

Thank you in advance for addressing Antares' request. Should you have any questions, please feel free to contact Dr. Dave or myself at any time.

Enjoy your long weekend.

Kind Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
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Best Regards,
nita

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Thank you.

Best Regards
Jerry

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From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Monday, November 07, 2011 3:08 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: NDA 202513 Anturof: carton/container labels

Hi Jerry,

Request below is from our Chemistry reviewer regarding the carton/container labeling. The comments from Division of Medication Error Prevention and Analysis (DMEPA) will follow in a separate email. Please revise your carton/container labeling accordingly and email the mock labels to me on/before 12:00 P.M. on November 10, 2011.

- 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:

Anturof
(oxybutynine) gel
3%
- All inactive ingredients should be described in the carton label per 21CFR 201.100(b)(5)

Thank you so much,
Nita

12/6/2011

Reference ID: 3058478

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

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



NDA 202513

TELECONFERENCE MEETING MINUTES

Antares Pharma, Inc.
Attention: Kaushik J. Dave, R.Ph., Ph.D., MBA
Senior Vice President, Product Development
250 Phillips Blvd.
Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Anturol (oxybutynin gel, 3%).

We also refer to the teleconference meeting between representatives of your firm and the FDA on March 30, 2011. The purpose of the meeting was to recommend amending the NDA application with respect to application type from a 505(b)(1) to 505(b)(2).

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nenita Crisostomo, R.N., Senior Regulatory Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Lynnda Reid, Ph.D.
Pharmacology and Toxicology Supervisor
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Teleconference Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Guidance
Meeting Date and Time: March 30, 2011@ 11:00 AM
Application Number: NDA 202513
Product Name: Anturol (oxybutynin gel, 3%)
Indication: treatment of overactive bladder
Sponsor/Applicant Name: Antares Pharma
Meeting Chair: Lynnda Reid, Ph.D.
Meeting Recorder: Eufrecina DeGuia

FDA ATTENDEES

Lynnda Reid, Ph.D. – Pharmacology and Toxicology Supervisor, Division of Reproductive and Urologic Products (DRUP)
Eufrecina DeGuia – Senior Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Kaushik Dave, RPH, Ph.D., MBA – Senior Vice President, Product Development
Gerry Orehostky - Vice President Quality and Regulatory Affairs

Background and Discussion:

NDA 202513 was submitted on December 2, 2010. On January 3, 2011, the applicant was notified that the NDA application was not accepted for filing due to non-payment of user fees. Antares Pharma was granted a small business waiver on February 8, 2011, therefore, the application was acceptable for review effective that date.

This NDA was submitted as a 505(b)(1) application based on the Agency's recommendation at the End of Phase 2 (EOP2) meeting held on May 2, 2006. (Please see EOP2 meeting minutes dated May 31, 2006).

Antares Pharma was informed via this brief phone call that at the Filing Meeting held on March 28, 2011, the Division determined that this application should be amended to be 505(b)(2); that this submission could not be filed under a 505(b)(1) because the company did not 'own' the necessary nonclinical data to support a stand alone application. Antares Pharma wished to use Ditropan as the RLD and the Division responded that we believed it to be an appropriate reference product. The applicant agreed to change the application type to 505(b)(2) with Ditropan 5mg as the RLD. We also requested them to submit their rationale for bridging to Ditropan 5 mg as the RLD, which they submitted on April 5, 2011.

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

/s/

LYNNDA L REID
11/17/2011

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, November 16, 2011 4:33 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturo: carton/container labels
Importance: High
Follow Up Flag: Follow up
Due By: Friday, November 18, 2011 3:30 PM
Flag Status: Flagged
Attachments: IR.DMEPA.carton.container.11.16.11.doc

Tracking:

Recipient	Read
'Gerald Orehostky'	
Kaushik Dave	
Fava, Walter	Read: 11/17/2011 5:40 AM
Kaul, Suresh	Read: 11/17/2011 8:39 AM
Kurtyka, Bogdan	Read: 11/17/2011 8:17 AM
Christner, Donna	Read: 11/16/2011 4:33 PM
Jarow, Jonathan	Read: 11/17/2011 7:59 AM
Hutchins, Shawna	Read: 11/17/2011 7:53 AM
Mena-Grillasca, Carlos	Read: 11/17/2011 11:00 AM
Maniwang, Janice	Read: 11/16/2011 6:34 PM
Kwak, Jina	

Hi Jerry,

Attached is our response to your version of the carton/container labeling. Please email to me your response, complete with mock labels, on or before November 18, 2011.

Thank you so much,
nita

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
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Enjoy your long weekend.

Kind Regards
Jerry

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12/6/2011

Reference ID: 3058478

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3%

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Thank you so much,

Nita

Nenita Crisostomo, RN

Regulatory Health Project Manager

U.S. Food and Drug Administration

Center for Drug Evaluation and Research

Division of Reproductive and Urologic Products

Telephone: 301-796-0875

Fax: 301-796-9897

12/6/2011

Reference ID: 3058478

FOOD AND DRUG ADMINISTRATION
Division of Reproductive and Urologic Products

NDA 202513 Anturol (oxybutynin) gel, 3%

FDA COMMENTS AND RECOMMENDATIONS

CARTON/CONTAINER LABELING

We refer to your November 11, 2011, email containing your version of the labeling in response to our November 7, 2011, recommendations. The Division of Medication Error Prevention and Analysis (DMEPA) recommends the following revisions because the presentation of important information is not optimal and the labels and labeling appear crowded. Please respond on or before close of business on November 18, 2011, via email complete with the mock labeling.

Container Labels

- Delete the company logo which appears at the top of the principal display panel next to the proprietary name, as it is duplicative and adds to the crowding of the label.
- Relocate the storage information and the 'Keep out of the reach of children statement' to appear at the bottom portion of the principal display panel following the statements, 'X g providing X metered doses' and 'Each metered-dose provides 0.9 g of gel containing 28 milligrams of oxybutynin'.
- Decrease the graphic at the bottom of the principal display panel to accommodate the relocation of the information above.

Sample Container Labels

- See container label comments above and implement accordingly on the principal display panel of the sample container
- Relocate the statement, 'Sample-Not For Sale', to the bottom portion of the principal display panel

Carton Labeling

- Consider de-bolding the storage information on the principal display panel and relocating it to the side panel as it crowds the label and will provide more room to make other information more prominent.
- Increase the font size and prominence of the statement, 'Each metered-dose provides 0.9 g of gel containing 28 milligrams of oxybutynin'.
- Relocate the company logo that appears above the proprietary name to the bottom portion following the 'Rx Only' statement and delete the small company logo

which appears at the bottom of the principal display panel as it is duplicative and difficult to read.

- If the Patient Package Insert is attached to the Professional Package Insert, remove the statement, 'Pharmacist: Please remove package insert before dispensing'.

Sample Carton Labeling

- See carton labeling comments above and implement accordingly.

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, November 16, 2011 12:46 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202-513: TCON w/ FDA
Sensitivity: Confidential

Hi Jerry & Kaushik,

We are available for tcon today at 2:15 - 3:00 pm. Please confirm if this is amenable to you.

Thank you so much,
 nita

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Tuesday, November 15, 2011 4:50 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: NDA 202-513: Final Draft - Proposed PI
Sensitivity: Confidential

Dear Nita,

Per Dr. Dave's direction, I am forwarding for the Agency's review, a proposed draft version of the ANTUROL Package Insert (PI). I have included a final version in MS Word format that contains no marked sections. This file is identified with the suffix "CLEAN" in the filename. Alternatively, I have also provided this same version of the ANTUROL PI in MS Word format, however, this version exhibits the various changes made to the document originally provided to Antares from the Agency on 07 November 2011. This file is identified with the suffix "TRACKED CHANGES". In addition, a document is also attached to this email that summarizes the changes made within the PI. Please note that all changes proposed by the Agency have been addressed although the Agency's original comments were retained in the TRACKED CHANGES version for convenience when reviewing.

In some cases, Antares Pharma has included comments to address Agency feedback or request further clarification regarding proposed changes. (b) (4)

Should you have any questions or wish to discuss further any items noted above, please feel free to contact Dr. Dave or myself at any time.

Antares Pharma thanks you and the review team for the collaborative and interactive nature of the review process experienced thus far.

Best Regards
 Jerry

12/6/2011

Reference ID: 3058478

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
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Office: 609 359 3033

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Thank you.

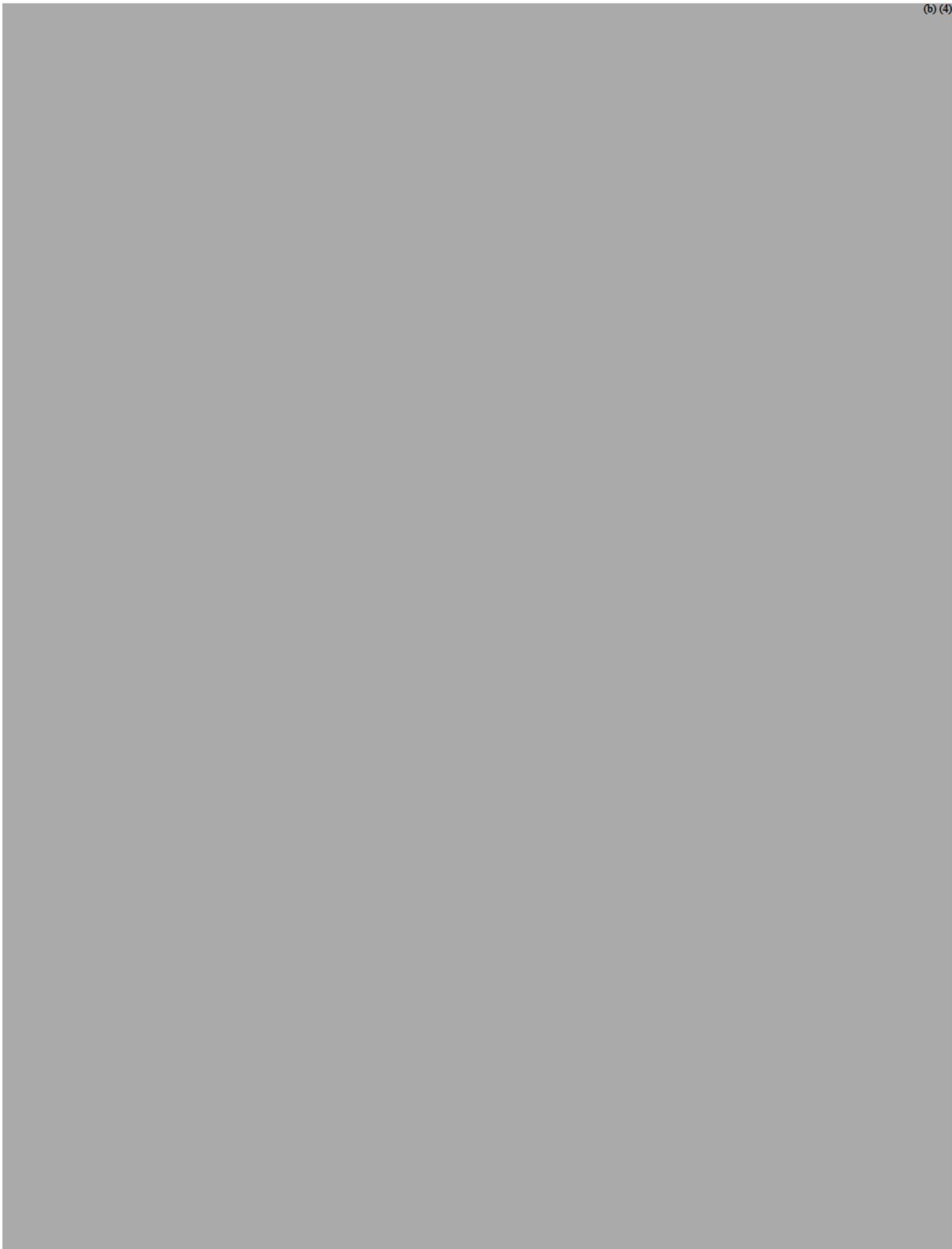
12/6/2011

Reference ID: 3058478

Summary of changes and comments to Pi provided by FDA on November 7, 2011:

SECTION	CHANGE(S) MADE	SUPPORTING DOCUMENTATION
Highlights of Prescribing Information	Accepted all changes (b) (4) (b) (4)	(b) (4)
Full Prescribing Information		
1. Indication and Usage	Accepted all proposed changes from the agency.	
2. Dosage and Administration	Accepted all changes (b) (4) (b) (4) (b) (4)	(b) (4)
3. Dosage Forms and Strengths	Accepted all changes (b) (4) (b) (4)	(b) (4)
4. Contraindications	Accepted all proposed changes from the agency and added cross reference.	
5. Warnings and Precautions	Accepted all proposed changes from the agency. (b) (4) (b) (4)	(b) (4)
6. Adverse Reactions	Accepted all proposed changes from the agency except: (b) (4)	See Table provided for Sponsor calculation
7. Drug Interactions	Accepted proposed numbering changes.	
8. Use in Specific Populations	Accepted all agency changes to Section 8.1. Anturoi is a 505(b)2 application using Ditropan as the RLD and hence this language. (b) (4) (b) (4)	(b) (4)
10. Overdosage	Accepted all agency changes.	

11. Description	Accepted all agency changes. (b) (4)	
12. Clinical Pharmacology	Accepted all agency changes. (b) (4)	
13. Nonclinical Toxicology	Accepted all agency changes.	
14. Clinical Studies	Accepted all changes with the agency. (b) (4)	(b) (4)
15. References	Accepted agency suggestion to remove (b) (4)	
16. How Supplied / Storage and Handling	Added NDC number and accepted all agency suggestions.	(b) (4)
17. Patient Counseling Information	Accepted all agency changes.	



Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Wednesday, November 16, 2011 12:27 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202-513: Final Draft - Proposed PI
Sensitivity: Confidential

Thank you so much, Jerry. We'll get back to you as soon as we can. Have a great day!
 --nita

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Tuesday, November 15, 2011 4:50 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: NDA 202-513: Final Draft - Proposed PI
Sensitivity: Confidential

Dear Nita,

Per Dr. Dave's direction, I am forwarding for the Agency's review, a proposed draft version of the ANTUROL Package Insert (PI). I have included a final version in MS Word format that contains no marked sections. This file is identified with the suffix "CLEAN" in the filename. Alternatively, I have also provided this same version of the ANTUROL PI in MS Word format, however, this version exhibits the various changes made to the document originally provided to Antares from the Agency on 07 November 2011. This file is identified with the suffix "TRACKED CHANGES". In addition, a document is also attached to this email that summarizes the changes made within the PI. Please note that all changes proposed by the Agency have been addressed although the Agency's original comments were retained in the TRACKED CHANGES version for convenience when reviewing.

In some cases, Antares Pharma has included comments to address Agency feedback or request further clarification regarding proposed changes. (b) (4)

Should you have any questions or wish to discuss further any items noted above, please feel free to contact Dr. Dave or myself at any time.

Antares Pharma thanks you and the review team for the collaborative and interactive nature of the review process experienced thus far.

Best Regards
 Jerry

Gerald J. Orehostky
 Vice President Quality and Regulatory Affairs
 Antares Pharma, Inc.
 250 Phillips Blvd

12/6/2011

Reference ID: 3058478

Suite 290
Ewing, NJ 08618
Office: 609 359 3033

(b) (6)

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12/6/2011

Reference ID: 3058478

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 07, 2011 4:06 PM
To: 'Gerald Orehostky'
Cc: 'Kaushik Dave'
Subject: RE: NDA 202513 Anturol: carton/container labels - DMEPA
Attachments: IR.DMEPA.carton labels.11.7.11 to sponsor.doc

Hi again, Jerry,

Attached in WORD are additional recommendations from the Division of Medication Error Prevention and Analysis regarding the carton/container labeling. As with my previous email containing the CMC carton labeling recommendations, please revise your carton/container labeling accordingly and email the mock labels to me on/before 12:00 P.M. on November 10, 2011.

If you have any questions, please feel free to contact me.

Best Regards,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

From: Crisostomo, Nenita
Sent: Monday, November 07, 2011 3:55 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturol: carton/container labels

Hi Jerry,

You are correct that oxybutynine is a typographical error. Please remove the "e" at the end. Thanks so much for bringing it to our attention.

Best Regards,
nita

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Monday, November 07, 2011 3:49 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturol: carton/container labels

Hello Nita,

I would appreciate clarification regarding one item. You indicated the Chemistry reviewer requested changes to the carton/container labeling. Please clarify whether the additional "e" at the end of the word "oxybutynine" was intentional or a typographical error.

Thank you.

Best Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
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Office: 609 359 3033 (b) (6)

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Monday, November 07, 2011 3:08 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: NDA 202513 Anturoi: carton/container labels

Hi Jerry,

Request below is from our Chemistry reviewer regarding the carton/container labeling. The comments from Division of Medication Error Prevention and Analysis (DMEPA) will follow in a separate email. Please revise your carton/container labeling accordingly and email the mock labels to me on/before 12:00 P.M. on November 10, 2011.

- 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:

Anturoi
(oxybutynine) gel
3%
- All inactive ingredients should be described in the carton label per 21CFR 201.100(b)(5)

Thank you so much,
Nita

Division of Medication Error Prevention and Analysis

NDA 202513 Anturol (oxybutynin) gel 3%

Recommendations for Carton/Container Labeling

Sent to Sponsor on November 7, 2011

A. General Comment

Remove all trailing zeros (i.e. change '3.0%' to '3%' and '1.0 mL' to '1 mL') throughout all labels and labeling. Trailing zeros are considered dangerous dose designations. DMEPA, consistent with recommendations from the Institute of Safe Medication Practices (ISMP) and the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), advises against the use of trailing zeros because they are error-prone and can result in a ten-fold misinterpretation if the decimal is not seen.

B. Carton Labeling (30 and 90 metered doses)

1. Increase the font size and the prominence of the proprietary name, established name, and strength. As currently presented, the route of administration, 'For Topical Use Only', has the greater prominence. The names and strength should be the most prominent information on the principal display panel.
2. Ensure the established name has the same prominence and type as the proprietary name per 21 CFR 201.10(g)(2).
3. Revise the presentation of the statement, 'X g providing X metered doses' so that the numerical quantifier does not appear at the end of a text line. For example:

"X g providing
90 metered doses"

or

"X g providing
30 metered doses"

4. Include a statement, 'Each metered dose provides X g of gel containing 28 milligrams of oxybutynin', on the principal display panel below the statement, 'X g providing X metered doses'.
5. Include a statement on the side panel to read, 'Recommended Dosage: See Prescribing Information'.
6. Consider including the statement, 'If Anturol gets in your eyes, thoroughly rinse your eyes right away with warm, clean water to flush out any Anturol. Seek medical attention if needed.'

C. Container Label

See comments B2 through B4 above and revise the container label accordingly.

If you have further questions or need clarifications, please contact Karen Townsend, project manager, at 301-796-5413.

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 07, 2011 2:40 PM
To: 'Gerald Orehostky'
Cc: 'Kaushik Dave'
Subject: RE: NDA 202513 Anturool: Patient Information
Attachments: NDA 202513 Anturool PPI 11 7 2011.to sponsor.doc

Hi Jerry,

As indicated in my previous email, attached are our recommendations to the Patient Information labeling. Please accept all of our marked edits and mark your edits, if any, on a clean version of the attached so that your edits can be visible for ease of review and provide justification of your counter-proposal as applicable.

Carton/container labeling recommendations will follow in a separate email.

Please email to me your response on/before close of business on close of business on Wednesday, November 9, 2011. If you have any questions, please feel free to contact me.

Thank you so much,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 07, 2011 2:15 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: NDA 202513 Anturol: Package Insert
Attachments: NDA 202513 Anturol PI 11 7 2011.to sponsor.doc

Hi Jerry,

Attached is our first version of the labeling: Package Insert, marked with our recommendations. Please accept all of our marked edits and mark your edits, if any, on a clean version of the attached so that your edits can be visible for ease of review and provide justification of your counter-proposal as applicable.

Patient Information and carton/container labeling recommendations will follow in a separate email.

Please email to me your response on/before close of business on close of business on Wednesday, November 9, 2011. If you have any questions, please feel free to contact me.

Thank you so much,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

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

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Monday, November 07, 2011 2:00 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: RE: Release rate specifications

Thank you so much, Jerry. We'll look out for your official submission.
--nita

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Monday, November 07, 2011 12:39 PM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: RE: Release rate specifications

Dear Nenita,

After speaking with Dr. Dave earlier today, Antares Pharma has agreed with the Agency's proposal of establishing interim ANTUROL finished product Release (Diffusion) Rate specification limits of (b) (4) (b) (4) for Release and Stability (Shelf-life). Once Antares has produced and analyzed ten (10) commercial ANTUROL batches, Release Rate specification limits will be re-assessed and submitted along with final specification limits.

As discussed during Antares-FDA teleconference of 02 November 2011, an official submission containing the agreed-upon interim Release Rate specification limits will be submitted to NDA 202-513 during the week of 07 November 2011.

Best Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033
(b) (6)

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Thank you.

12/6/2011

Reference ID: 3058478

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Friday, November 04, 2011 3:14 PM
To: Kaushik Dave
Cc: Gerald Orehostky
Subject: RE: Release rate specifications

Hi Kaushik,

The Agency has reviewed the information you provided and proposes an interim 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.

Thank you so much and have a great weekend!
--nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Friday, November 04, 2011 11:00 AM
To: Crisostomo, Nenita
Cc: Gerald Orehostky
Subject: Release rate specifications
Importance: High

Nita,

Pursuant to our telephone call on November 2, 2011, Antares is submitting a proposal for release rate specification for ANTUROL. Please forward this to Dr. T. Ghosh and if he would like to discuss this further, we are available today at 2:00PM to have a teleconference to finalize the specifications. We would appreciate a confirmation of concurrence from the agency today with Antares' proposed specifications so that we can start updating the appropriate NDA sections for submission next week.

Antares will also be emailing latter today, per our commitment, the updated Attachment 2 from SN0012, and the investigation report.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020

(b) (6)

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Thank you.

12/6/2011

Reference ID: 3058478



Antares Pharma, Inc.
Princeton Crossroads Corporate Center
Phillips Boulevard, Suite 290
Ewing, NJ 08618

Tel. (609) 359-3020
Fax (609) 359-3015

**ANTARES PHARMA INC.
NDA 202-513
ANTUROL Drug Product Release Rate Specification Limit Recommendation
04 November 2011**

On 02 November 2011, Antares Pharma and FDA engaged in a teleconference to discuss the topic of its ANTUROL NDA 202-513, Amendment SN0012. The subject of this amendment is the Diffusion Release Rate product parameter established to monitor ANTUROL product quality at the time of initial product disposition and over product shelf-life. Diffusion Release Rate is a measurable characteristic of the drug product utilized to assess product quality, therefore, Antares Pharma has proposed drug product release and shelf-life (stability) specification limits for this parameter. The Diffusion Release Rate specification limits were a key subject of discussion during the 02 November 2011 teleconference previously mentioned. In particular, the Division indicated that the specification limits proposed by Antares Pharma in the SN0012 amendment were not consistent with the limits expected by the Division. At the conclusion of the teleconference, the Division and Antares Pharma agreed that Antares was to provide response offering either concurrence with the Diffusion Release Rate specification limits proposed by the Division or provide a counter-proposal for these limits. It was agreed that concurrence or a counter-proposal would be provided by Antares on Friday, 04 November 2011 via email followed by official amendment to NDA 202-513 during the week of 07 November 2011. During a post-teleconference telephone discussion with Nenita Crisotomo, RN from the Division, it was also agreed that Antares' would provide the Division with a response on Friday, 04 November 2011 prior to noon to permit a teleconference in the afternoon of the same day, if necessary. The purpose of this planned teleconference is to permit Dr. Ghosh, who had previously requested a meeting with Antares' Statisticians, an opportunity to interface with the statisticians and to discuss Antares' response. The purpose of this teleconference is to reach a final agreement on Diffusion Release Rate specification limits prior to submitting the official amendment to NDA 202-513 during the week of 07 November 2011. The information below is intended to address the aforementioned agreement and provide Antares' response regarding Diffusion Release Rate specification limits.

Antares Pharma had proposed

[Redacted content] (b) (4)

[Redacted content] (b) (4)

[Redacted content]

Per the Division's recommendation in a Request for Information dated 07 October 2011, Antares Pharma calculated the 90% Confidence Interval (CI) to establish a basis for proposing alternative

Diffusion Release Rate specification limits.

(b) (4)

[Redacted]

[Redacted]

(b) (4)

In the meeting held November 2, 2011 ,the agency presented their 90% CI

(b) (4)

[Redacted]

This 90% CI is also known as the 90% CI of the mean.

[Redacted]

(b) (4)

Response Item #4, Table 1: Statistical summary and proposed diffusion rate specifications for release and stability



Furthermore, as part of routine continuous improvement initiatives, Antares commits to evaluate and further modify Diffusion Release Rate specification limits after additional results have been generated for the first ten (10) batches of commercial product, if so warranted by the data.

Both approaches presented above support the proposed specifications of [redacted] (b) (4). Furthermore, as part of routine continuous improvement initiatives, Antares commits to evaluate and further modify Diffusion Release Rate specification limits after additional results have been generated for the first ten (10) batches of commercial product, if so warranted by the data.

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Friday, November 04, 2011 3:22 PM
To: 'Kaushik Dave'
Cc: Gerald Orehostky
Subject: RE: NDA 202513 Anturo: TCON Discussion Items
Attachments: Disc items.SAP.multiplicity.to.sp.11.9.11.tcon.doc

Hi Kaushik,

Attached contains the agenda for our discussion on our scheduled 11/9/11 teleconference with you and your Team

Thank you so much,
nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Thursday, November 03, 2011 11:38 AM
To: Crisostomo, Nenita
Subject: RE: NDA 202513 Anturo: TCON Request

I will work very hard to make this happen. Please provide me a list of items for discussion. This will help identify which consultants I really need. Thanks for your understanding.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020


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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, November 03, 2011 11:35 AM
To: Kaushik Dave

12/6/2011

Reference ID: 3058478

Subject: RE: NDA 202513 Anturol: TCON Request

Thank you. As we are nearing the Action Date and with certain issues that yet need to be resolved, it gets harder to find available meeting slots common for all of our team members who are working on multiple applications at the same time, and therefore, just as busy. But knowing the critical nature of our review, we see the need to accommodate. Thanks again for considering. I'll wait for your confirmation.

--nita

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Thursday, November 03, 2011 11:30 AM
To: Crisostomo, Nenita; Gerald Orehostky
Subject: RE: NDA 202513 Anturol: TCON Request

Nita,

Thanks for changing the Tcon day. I have reached out to our consultants to determine their availability. I will get back to you latter. However, these consultants are very busy.

Regards,

Kaushik
 Kaushik J. Dave R.Ph.,Ph.D.,MBA
 Executive Vice President Product Development
 250 Phillips Blvd Suite 290
 Ewing, NJ 08618
 Phone: 609 359 3020

(b) (6)

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Thursday, November 03, 2011 11:11 AM
To: Kaushik Dave; Gerald Orehostky
Subject: NDA 202513 Anturol: TCON Request

Hi Kaushik & Jerry,

Thank you for letting us know about Monday. We have changed our TCON Request for Wednesday, Nov 9, 2011, at 1:00pm to 2:00pm. Please confirm.

Please use this Call-in#: 1-866-643-3861, Participant Passcode: (b) (4)

Thank you,
 nita

12/6/2011

Reference ID: 3058478

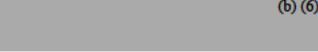
Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Wednesday, November 02, 2011 9:18 PM
To: Crisostomo, Nenita
Subject: TCON for Monday

Nita,

I just remembered that I am travelling on business next Monday and hence will be out of the office. I am available any other day next week. Please let me know as soon as possible which day works for you and your colleagues so that I can check with the consultants. My biostats consultants are very difficult to get since they are busy.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020


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Thank you.

12/6/2011

Reference ID: 3058478

FOOD AND DRUG ADMINISTRATION
Division of Reproductive and Urologic Products

NDA 202513 Anturol (oxybutynin) gel, 3%

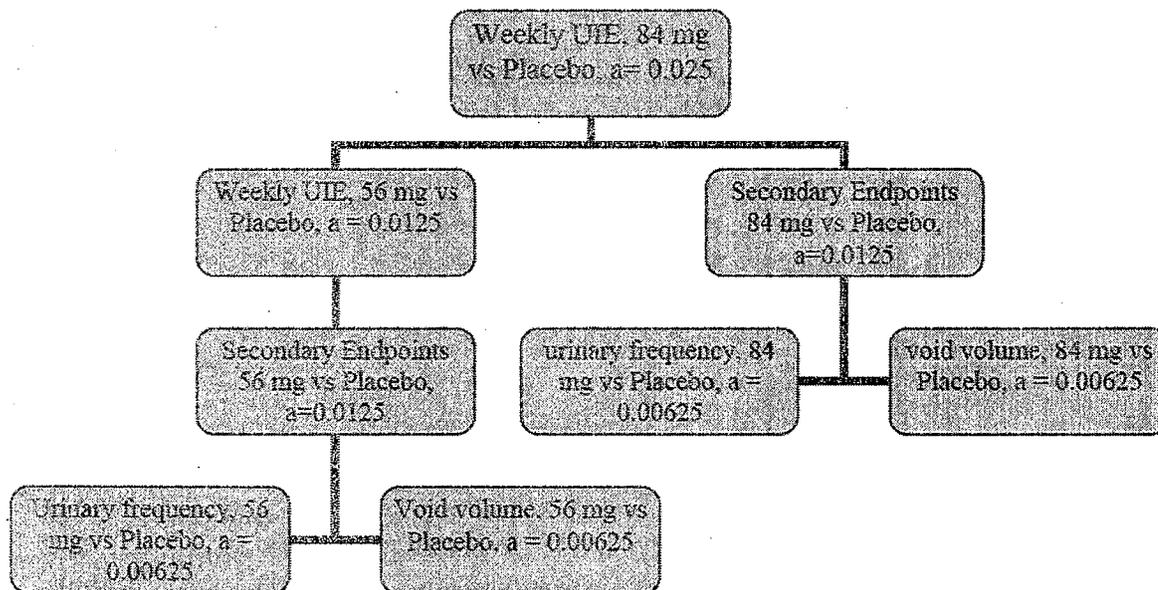
DISCUSSION ITEMS

For November 9, 2011, at 1:00 P.M. – 2:00 P.M. Teleconference

During the NDA 202513 review process, two testing procedures on multiplicity control of overall type I error in Study 20070060 were noted. Figures A and B are diagrams of the two testing procedures, for which the pertinent information is summarized below.

1. Figure A is the diagram of the testing procedure that was described on Page 34 in the statistical analysis plan (SAP) dated June 10, 2010.
 - This statistical analysis plan was submitted to FDA on August 26, 2010, and according to the cover letter, this was the “final executed” SAP.
 - The same SAP was submitted as part of the Study 20070060 report (Appendix 16.1.9) in the NDA submission.

Figure A: Testing procedure in the final SAP dated June 10, 2010

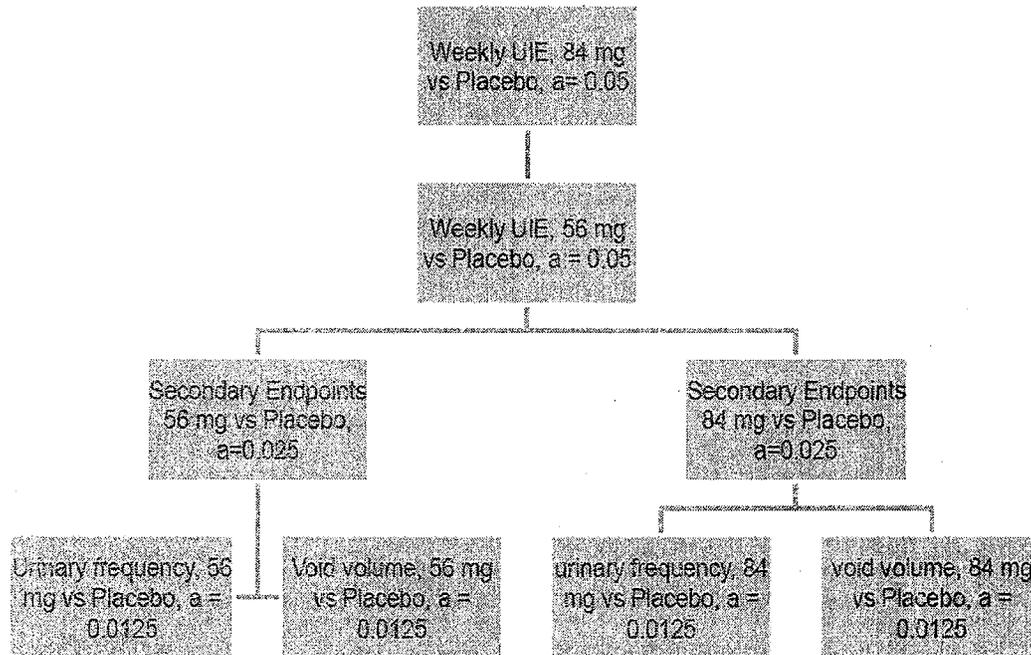


(Note: α is for one-sided test)

2. Figure B is the diagram of the testing procedure that was described in the Sponsor's response (dated October 06, 2011) to FDA's e-mailed information request for clarification on the final SAP.

- In Appendix 16.1.9 of the 20070060 study report, the sponsor also provided a memorandum on "clarifying roles of closed testing of two doses versus placebo for primary endpoint and amended strategy for controlling type I error for secondary clinical endpoints". This memorandum was dated August 24, 2010.
- Figure B described the strategy in this memo.

Figure B: Testing procedure in the sponsor's e-mailed response dated October 6, 2011



(note: α is for two-sided test)

Crisostomo, Nenita

From: Crisostomo, Nenita
 Sent: Thursday, November 03, 2011 5:12 PM
 To: 'Kaushik Dave'
 Cc: Gerald Orehostky
 Subject: FW: NDA 202513 Anturoi: Antares requests a toon w/ BioPharm

Hi Kaushik/Jerry,

Dr. Gosh, the Biopharmaceutics reviewer, used JMP 9.0.2 version to come up with the following table based on your data. Your mean and SD data matched except inclusion of Oxyg22303 batch data for release. Only 90% CI differed a little. Hope this helps. Our review of your proposal that you will email to me tomorrow will determine whether we still need your requested teleconference or not.

Release:

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

Stability:

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

Thank you so much,
 nita

Nenita Crisostomo, RN
 Regulatory Health Project Manager
 U.S. Food and Drug Administration
 Center for Drug Evaluation and Research
 Division of Reproductive and Urologic Products
 Telephone: 301-796-0875
 Fax: 301-796-9897

From: Kaushik Dave [mailto:kdave@antarespharma.com]
Sent: Thursday, November 03, 2011 2:27 PM
To: Crisostomo, Nenita
Subject:
Importance: High

Nita,

I am working on the diffusion specifications document which I hope to send first thing tomorrow morning for you to forward it to Dr. Ghosh. This will have an explanation on how we calculated the 90% CI. I would like to suggest we have a call between Dr. Ghosh, and myself plus our statistics consultant so that we can agree on the final specifications. We need to get this done so that we can update the NDA in one single step for next week. We are available tomorrow at 2PM for a call. Please let me know if that works for Dr. Ghosh and you.

Thanks.

Regards,

Kaushik
Kaushik J. Dave R.Ph.,Ph.D.,MBA
Executive Vice President Product Development
250 Phillips Blvd Suite 290
Ewing, NJ 08618
Phone: 609 359 3020

(b) (6)

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Thank you.

12/6/2011

Reference ID: 3058478

Crisostomo, Nenita

From: Crisostomo, Nenita
Sent: Thursday, October 27, 2011 4:30 PM
To: 'Gerald Orehostky'
Cc: 'Kaushik Dave'
Subject: RE: NDA 202513 Anturoi: CMC/BioPharm - TCON Request
Attachments: BP.Discussion pts for 11.2.11 tcon.doc

Hi Jerry,

I am following up on your confirmation of our proposed TCON on Nov 2, at 12:30 pm - 1:30 pm, Eastern Time. Please confirm.

Attached is our Discussion Points for the TCON.

Thank you so much,
nita

From: Crisostomo, Nenita
Sent: Wednesday, October 26, 2011 4:54 PM
To: 'Gerald Orehostky'
Cc: Kaushik Dave
Subject: NDA 202513 Anturoi: CMC/BioPharm - TCON Request

Hi Jerry,

As I mentioned to Dr. Dave in a phone call a moment ago, our CMC Team is requesting a tcon with your Team, specifically, with your CMC/Product Quality/BioPharm Team to discuss your most recent submission.

Please confirm this proposed meeting date/time:

Wednesday, November 2, 2011, at 12:30 - 1:30 pm.

Thank you,
nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

NDA 202513
Anturol (oxybutynin) gel, 3%

DISCUSSION POINTS for
November 2, 2011 Teleconference, at 12:30 P.M. – 1:30 P.M.

To the Sponsor: In reviewing your response dated September 22, 2011, to our Information Request letter dated September 7, 2011, we noted that the slopes calculated for lot HKB (as shown in the Attachment 1 below) are incorrect. It appears that the results for Batch # HKM are in the Batch # R0266B003. Additionally, we noted that the raw data submitted for two different batches (Attachment 2 below) are exactly the same. We would like an explanation for this and your plan of action to deal with this issue.

(b) (4)







NDA 202513

INFORMATION REQUEST

Antares Pharma, Inc.
Attention: Kaushik J. Dave, Ph.D., Senior VP Product Development
250 Phillips Boulevard, Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for oxybutynin gel 3.0%.

We also refer to your submission dated December 20, 2010.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by October 11, 2011 in order to continue our evaluation of your application. Please send your response via email to rebecca.mcknight@fda.hhs.gov as well as sending an amendment to your application.

1. Please submit raw data (in electronic format) from each cell at each time point used to calculate the slope (diffusion rate) for each formulation at the different stability times.
2. Clearly describe the method and associated data used to calculate the slope and RSD values used in Table 1 and Table 2 in the Statistical Specifications Calculation. Also, please clarify your intent (how and why) to use the "Diffusion Rate: RSD" as part of your release and stability specifications.
3. Explain how you came up with a "*a priori*" acceptance criteria for slope and RSD values.
4. [REDACTED] (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's specifications.
6. Please explain why the value of slope [REDACTED] (b) (4) for the batch "HKC" as submitted in the original submission is different [REDACTED] (b) (4) in the amendment submitted on 8/5/11 in Table 41.

7. In your stability report – 2011-001 Ver. 00 dated 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)

[REDACTED]

Please, provide the *in-vivo* data assuring that product batches with such different viscosities and diffusion rates will have similar *in-vivo* performance (e.g., bioavailability, efficacy and safety). Also, describe what steps you are planning to take to control the grades of (b) (4) to-be-used in your commercial product, in order to have a tighter control of your product's quality/performance.

8. Please provide an update of your response to our September 19, 2011 IR Letter.

If you have questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{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
Center for Drug Evaluation and Research

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/s/

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 6, 2011

TO: Memo to File

THROUGH : Suresh Kaul, M.D. – Clinical Team Leader

FROM: Nenita Crisostomo, R.N. - Regulatory Health Project Manager

SUBJECT: Statistical Analysis Plan for Study 20070060

APPLICATION/DRUG: NDA 202513 Anturol (oxybutynin) gel, 3%

Background: On October 5, 2011, a teleconference was held with Antares Pharma to provide an update regarding the labeling which will include efficacy information on the 84 mg dosage only. Following the teleconference, an email was sent to the sponsor requesting clarification on which final statistical plan was used for Study 20070060 and responded with the October 6, 2011, email with a written clarification statement, as attached.

From: Gerald Orehostky [mailto:gorehostky@antarespharma.com]
Sent: Thursday, October 06, 2011 10:57 AM
To: Crisostomo, Nenita
Cc: Kaushik Dave
Subject: RE: NDA 202513 Anturol: SAP

Dear Nita,

You are quite welcome, and as noted in my previous email, we certainly appreciate your team's openness and keeping us apprised of major issues that arise.

With respect to your question regarding the final Statistical Analysis Plan (SAP), the final SAP is identified as Version 3.0 and is dated 10 June 2010. More detailed information relating to this question is provided in the attached summary discussion prepared by Dr. Dave. This discussion provides additional clarity regarding the Final SAP.

We would appreciate if you could forward the attached summary discussion to members of the DRUP Review Team involved in the evaluation of the Anturol pivotal clinical study outcomes and data such as Drs. Kaul and Jarow and, any other pertinent clinical reviewers and biostatistician Team members.

Should you have any questions or require additional information, please do not hesitate to contact me. Also, should anyone require additional clarification regarding the attached summary discussion, please let me know and, Dr. Dave and I will be available at your convenience.

Once again, thank you for facilitating the very valuable teleconference we had yesterday and all of your efforts serving as Antares' RPM.

Have a great day.

Best Regards
Jerry

Gerald J. Orehostky
Vice President Quality and Regulatory Affairs
Antares Pharma, Inc.
250 Phillips Blvd
Suite 290
Ewing, NJ 08618
Office: 609 359 3033

(b) (6)

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Thank you.

From: Crisostomo, Nenita [mailto:Nenita.Crisostomo@fda.hhs.gov]
Sent: Wednesday, October 05, 2011 2:04 PM
To: Gerald Orehostky
Cc: Kaushik Dave
Subject: NDA 202513 Anturool: SAP

Hi Jerry,

Thanks again for the opportunity to discuss the label with you and Dr. Dave this afternoon.

We have question from our Team:

Please clarify what was your final statistical plan for Study 20070060?

Thank you so much,
Nita

*Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897*

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/s/

NENITA I CRISOSTOMO
11/16/2011



NDA 202-513

INFORMATION REQUEST

Antares Pharma, Inc.
Attention: Kaushik J. Dave, RPh, Ph.D., MBA
Senior Vice President Product Development
250 Philips Blvd., Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for oxybutynin gel 3%.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Please update your NDA per DMF (b)(4) for the current information on container closure system.

If you have any questions, call Becky McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
09/19/2011
Chief, Branch IV



NDA 202513

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Antares Pharma
Attention: Kaushik J. Dave, RPh, Ph.D., MBA
Senior Vice President Product Development
250 Phillips Blvd., Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for oxybutynin gel 3%

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have any questions, call Nenita Crisostomo, Senior Regulatory Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
08/30/2011
signed for Scott Monroe



NDA 202513

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Antares Pharma, Inc.
250 Phillips Boulevard, Suite 290
Ewing, New Jersey 08618

ATTENTION: Kaushik J. Dave RPh, PhD, MBA
Senior Vice President, Product Development

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) dated December 20, 2010, received December 21, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Gel, 3%.

We also refer to your May 5, 2011, correspondence, received May 5, 2011, requesting review of your proposed proprietary name, Anturol. We have completed our review of the proposed proprietary name, Anturol, and have concluded that it is acceptable.

The proposed proprietary name, Anturol, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 5, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Nenita Crisostomo at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
07/29/2011

Crisostomo, Nenita

From: Crisostomo, Nenita
Date: Friday, July 15, 2011 1:58 PM
To: 'Gerald Orehostky'
'Kaushik Dave'
Subject: NDA 202513 -Oxybutynin Gel 3% - BioPharm Information Request

Hi Jerry:

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

- (b) (4)
-
-
-
-
-
-
-
-

The Agency acknowledges the validation report. If the sponsor has already submitted the requested information (i.e., development report), please provide the submission date and direct us to the proper section of the submission.

Please submit your response to our request on/before July 22, 2011. If you have any questions, please feel free to contact me.

Thank you very much,

Nenita Crisostomo, RN
Regulatory Health Project Manager
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
Telephone: 301-796-0875
Fax: 301-796-9897

Tracking:	Recipient	Read
	'Gerald Orehostky'	
	'Kaushik Dave'	
	Ghosh, Tapash	Read: 7/15/2011 2:21 PM
	Kaul, Suresh	
	Jarow, Jonathan	Read: 7/15/2011 2:41 PM



NDA 202513

FILING COMMUNICATION

Antares Pharma
Attention: Kaushik J. Dave, RPh, Ph.D., MBA
Senior Vice President Product Development
250 Phillips Blvd., Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your New Drug Application (NDA) dated December 20, 2010, received February 8, 2011, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for oxybutynin gel 3%.

We also refer to your amendment dated March 10, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 8, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 20, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. Submit color mock-ups of all carton/container labels to allow full review and update all labeling with the appropriate NDC numbers.
2. Submit tabulation data (i.e. raw data), statistical programs to derive the efficacy endpoints and population flags, and statistical programs to carry out efficacy analyses of primary and secondary endpoints.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The Highlights section is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested in this application.
2. A horizontal line must separate the Table of Contents (TOC) and Full Prescribing Information (FPI).
3. Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms such as “adverse events” or “treatment-emergent adverse events” should be avoided.
4. For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:
“Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials on another drug and may not reflect the rates observed in clinical practice.”

We request that you resubmit labeling that addresses these issues three weeks from the date of this letter. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Eufrecina DeGuia, Senior Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

George Benson, M.D.

Deputy Director

Division of Reproductive and Urologic Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research



NDA 202513

INFORMATION REQUEST

Antares Pharma, Inc.
Attention: Kaushik J. Dave, Ph.D., Sr. VP Product Development
250 Phillips Boulevard, Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Anturool (oxybutynin) Transdermal Gel.

We also refer to your submission dated December 20, 2010.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

1. Your proposed limit for USP<755> Minimum Fill test is (b) (4) container and (b) (4) container (with fill target of (b) (4)). Revise the specifications as follows per USP<755>:
 - a. Include limits for average and individual containers
 - b. Reflect (b) (4) limits in the specification
2. Your proposed discontinuation of testing for (b) (4) in future stability studies is not acceptable. You may file an appropriate supplement post-approval after collecting sufficient supporting data.
3. Submit validation protocol and report for (b) (4) assay in drug product.
4. Regarding stability results:
 - a. The result stated for color attribute (b) (4) will be deemed out of specification (b) (4) and the expiration dating period will be determined accordingly, unless you provide justification.
 - b. Similarly, (b) (4) will be deemed out of specification with respect to the specification limit (b) (4)

standards, and therefore will also be taken into consideration for the calculation of the expiration dating period.

c.



If you have questions, call Rebecca McKnight, Regulatory Project Manager, at (301) 796-1765.

Sincerely,

{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
Center for Drug Evaluation and Research

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/s/

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

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/s/

GEORGE S BENSON
04/06/2011



NDA 202513

RECEIPT OF USER FEES

Antares Pharma, Inc.
Attention: Kaushik J. Dave, R.Ph., Ph.D., MBA
Senior Vice President, Product Development
250 Phillips Blvd.
Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Anturol (oxybutynin 3% gel).

You were notified in our letter dated January 3, 2011, that your application was not accepted for filing due to non-payment of fees. The Division has been notified that your request for small business waiver of the application fee for NDA 202513 has been granted on February 8, 2011, therefore, your application is now acceptable for review effective that date.

Unless we notify you within 60 days of the above date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 9, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, contact Eufrecina DeGuia, Senior Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
02/15/2011



NDA 202513

UNACCEPTABLE FOR FILING

Antares Pharma, Inc.
Attention: Kaushik J. Dave, R.Ph., Ph.D., MBA
Senior Vice President, Product Development
250 Phillips Blvd.
Suite 290
Ewing, NJ 08618

Dear Dr. Dave:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Anturol (oxybutynin 3% gel)

Date of Application: December 20, 2010

Date of Receipt: December 20, 2010

Our Reference Number: NDA 202513

We have not received the appropriate user fee for this application. An application is considered incomplete and cannot be accepted for filing until all fees owed have been paid. Therefore, this application is not accepted for filing. We will not begin a review of this application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 70963
Charlotte, NC 28272-0963

Checks sent by a courier should be addressed to:

Wells Fargo Bank
Attn: Food and Drug Administration, Lockbox 70963
1525 West WT Harris Blvd, Room D1113-022
Charlotte, NC 28262

NOTE: Please include the User Fee I.D. Number, the Application number, and the FDA P.O. Box number (P.O. Box 70963) on the enclosed check. It would be helpful if you included the user fee cover sheet (Form FDA 3397) with your payment.

The receipt date for this submission (which begins the review for filability) will be the date the review division is notified that payment has been received by the bank.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you wish to send payment by wire transfer, or if you have any other questions, please call Beverly Friedman or Mike Jones at (301) 796-3602.

If you have any questions, contact Eufrecina DeGuia, Senior Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER L MERCIER
01/03/2011

DRAFT Responses/Comments to Sponsor's Questions

Application: IND 70,527
Drug: Oxybutynin Gel, 3.0%
Sponsor: Antares Pharma, AG
Meeting Type: C
External Meeting: 10/27/09

*Note to Sponsor: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **October 27, 2009, 2:30 p.m. Eastern Time**, between **Antares Pharma** and the Division of Reproductive and Urologic Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference (contact Meredith Alpert, Regulatory Health Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your questions and development plans, based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting.*

SPONSOR'S QUESTIONS AND THE DIVISION'S COMMENTS

1. *The bridging data support pooling the data from the 130 patients generated with the previous formulation with the rest of the data (about 480 patients) generated with the modified formulation. Does the Division concur (please see briefing package for rest of data to question)?*

Division's Response:

We agree that the phase 3 data from the two formulations can be pooled. Please include a flag designating if the subject received the old or new formulation of the drug product in all datasets that are submitted with the NDA.

2. *In the preliminary draft responses for the 2 May 2006 End of Phase 2 Meeting, "Additional Clinical Comments regarding the proposed Phase 3 trial" comment A6, the Division requested that Antares collect open label safety extension data from at least 50 subjects for 6 months of active treatment to assess skin tolerability. Antares believes with the recent approval of Gelnique, a long term safety study for Anturool gel on 50 patients for 6 months should not be necessary since oxybutynin safety via the transdermal route has been established by Gelnique. Does the Division concur (please see briefing package for rest of data to question)?*

Division's Response:

This approach is acceptable but would necessitate your submitting your marketing application via the 505(b)(2) filing pathway. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. In the preliminary draft responses for the 5 Feb 2005 Pre-IND Meeting, Question 7, comments 2-6, the Division suggests that additional PK studies might be needed, to address issues including the possible transfer of the gel, the use of other topical agents as sunscreen, and washing procedures. Antares believes that there should be no need to conduct these special studies since Gelnique has performed these studies with transdermal oxybutynin gel. Does the Division concur? If the Division does not concur, can these studies be performed post approval of Anturol (please see briefing package for rest of data to question)?

Division's Response:

No, we do not concur.

(b) (4)

(b) (4)

. We continue to advise you to conduct these Phase 1 studies using your proposed formulation. Data should be included in the NDA at the time of submission.

4. Antares believes that the 2 batches at about (b) (4) scale and a third batch at (b) (4) manufactured support registration of Anturool. Does the Division concur (please see briefing package for rest of data to question)?

Division's Response:

We do not concur that stability data on two batches manufactured at the (b) (4) facility and the one batch manufactured at the (b) (4) facility will be adequate to support registration. For the primary stability batches, the batches should all be manufactured at the proposed commercial facility and should be packaged in the proposed to-be-marketed container closure system. Assuming that the (b) (4) facility is the proposed commercial facility, the data on the drug product manufactured at (b) (4) can be used as supportive data, as can the data gathered on the original formulation. We have the following additional comments:

- The change in manufacturing site from (b) (4) will need to be supported by comparative in vitro release testing
- Expiry will be set based upon review of the primary stability data, taking into account the supporting stability data
- Please confirm that the Content Uniformity test performed on stability is a Pump Performance test and that samples are taken throughout the container
- Please confirm that the Drug Release/In-vitro release test is performed at release and at all stability time points

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-70527

GI-1

ANTARES
PHARMA

OXYBUTYNIN GEL 3.0%

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

/s/

MEREDITH H ALPERT
10/22/2009

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End-of-Phase 2 (EOP-2) Meeting Minutes

EOP-2 Meeting: Oxybutynin Gel for the treatment of overactive bladder (OAB)

Sponsor: Antares Pharma **Date:** May 2, 2006

Time: 1:00 – 2:30 PM **Location:** White Oak Building, Conference Room
1311

FDA/CDER/DRUDP Attendees:

George Benson, M.D., Urology Team Leader, Division of Reproductive and Urologic
Products (DRUP; HFD-580)

Olivia Fasley, M.D., Medical Reviewer, DRUP

Sandhya Apparaju, Ph.D., Clinical Pharmacology Reviewer, OCPB @ DRUP

Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUP

Laurie McLeod-Flynn, Ph.D., Pharmacology/Toxicology Reviewer, DRUP

Sonia Castillo, Ph.D., Statistical Reviewer, Division of Biometrics 2, (HFD-175)

Jean Makie, M.S., R.D., Senior Regulatory Project Manager, DRUP

Ayoub Suliman, Pharm.D., Regulatory Project Manager, DRUP

Industry Attendees:

Jack Stover, President and CEO, Antares Pharma AG

Dario Carrara, Ph.D., Managing Director, Swiss Operations, Antares Pharma AG

Holger Kraus, Ph.D., Project Manager, Antares Pharma AG

(b) (6)

(b) (6)

Background: On March 22, 2006, the Sponsor submitted the following questions in their briefing package to the Division. The Division's preliminary draft responses were faxed to the Sponsor on April 27, 2006. Additional discussions held during the conduct of the meeting are also summarized below under "Sponsor Response," and/or "Division

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Comments." Specific questions are grouped by discipline as presented in the Sponsor's briefing package.

Division of Reproductive and Urologic Products

1. Does the Agency concur that the Phase 3 protocol can be flexible to account for a lower or higher oxybutynin dose, and that the sample size can likewise be adjusted in order to adequately power the study to account for this new dose?

Division Response: No. The Division does not concur that the oxybutynin dose or the sample size may be adjusted after the trial has started.

2. The Agency indicated in the Pre-IND meeting (PIND 70,527; February 9, 2005) that the transdermal product (Oxytrol) is the most appropriate reference oxybutynin formulation for a 505(b)(2) regulatory submission and that no active control arm is required by the Division.
 - a. If an oxybutynin gel product comes on the market during the Antares clinical development program or during the review time of Antares' NDA by FDA, will a change in the reference listed drug be necessary?

Division Response: Following further internal discussion, the Division currently believes that the 505(b)(1) regulatory pathway is an acceptable route for your product development. Your original proposal for a 505(b)(2) application would require referencing another NDA in order to support the characterization of oxybutynin as an active pharmaceutical ingredient. Because oxybutynin has been used clinically for many years and there is a significant body of knowledge associated with its use, the Division believes that a portion of the information usually required for drug approval by the 505(b)(1) route can be waived for oxybutynin. Specifically, no oxybutynin pharmacology/toxicology data would be required to be submitted. The efficacy and safety data submitted to support approval of oxybutynin gel would "stand alone" in support of drug approval.

If, after considering the 505(b)(1) option, you continue to find the 505(b)(2) regulatory pathway to be most appropriate for your future drug development efforts, then we remind you of the following points:

- **the 505(b)(2) regulatory pathway for all products is continually evolving and advice provided today is based on current standards, which may or may not be applicable when a Sponsor submits an NDA;**

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- **Sponsors must reference the most similar predicate product(s) when submitting a 505(b)(2) application;**
- **should a more appropriate reference product(s) be approved by the Agency at any time before or during the review of their NDA, a Sponsor would be required to submit a new application referencing the more appropriate product;**
- **the Agency can not disclose whether such a predicate product(s) is under development or has been submitted at any time during another Sponsor's review cycle.**

Sponsor Response: The Sponsor stated they will pursue the 505(b)(1) pathway.

- b. If Watson Pharmaceuticals, Inc. markets both the oxybutynin gel product and oxybutynin transdermal product (Oxytrol), will a change in the reference listed drug be necessary?

Division Response: See response to 2a above.

- c. If Watson Pharmaceuticals, Inc. replaces Oxytrol with the new oxybutynin gel product, will a change in the reference listed drug be necessary?

Division Response: See response to 2a above.

3. Is the Agency in agreement that a (b)(4) waiver for pediatric studies (b)(4) is acceptable?

Division Response: Yes.

4. Does the Agency concur that (b)(4) until after product approval is reasonable?

Division Response: Yes.

Medical Discipline

5. Does the Agency concur that the study design, number of patients, and treatment arms in the Phase 3 study are sufficient for establishing efficacy for oxybutynin gel?

Division Response: The design and sample size of the proposed Phase 3 study is acceptable. The Division recommends that two Phase 3 studies be performed. Alternatively, one study which demonstrates conclusive results could be submitted.

Sponsor Response: The Sponsor asked for clarification of "conclusive results."

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Division Comment: To be considered conclusive, a single efficacy trial would have to be both clinically and statistically significant. The definition of "clinically significant" will be a review issue.

Regardless of the regulatory pathway [505(b)(1) or 505(b)(2)] chosen for the NDA submission, the Division stated that it prefers two efficacy trials be submitted to support reproducibility of results. Borderline significant results from a single efficacy trial can pose review issues and is a risk a Sponsor assumes when conducting only a single efficacy study.

Sponsor Response: The Sponsor stated they will take the Division's recommendations into consideration in deciding whether they will conduct a single or two Phase 3 trials.

6. Is the Agency in agreement that the treatment arms (84 mg oxybutynin and placebo) in the proposed Phase 3 clinical trial are acceptable?

Division Response: The Division agrees with the selection of the 84 mg oxybutynin treatment arm but recommends that the (b) (4) also be investigated in order to establish a dose with the most favorable risk/benefit profile.

Sponsor Response: The Sponsor asked for clarification regarding the addition of a (b) (4).

Division Comment: The Division stated that the Sponsor's current drug development plan does not include any pharmacodynamic (PD) data to support efficacy of the 84 mg dose or improved efficacy of the 84 mg dose over the (b) (4). Studying only the 84 mg dose, which may have an unacceptable side effect profile, is the sponsor's risk and may be a review issue at the time of NDA submission. The Division believes that it is to the Sponsor's advantage to also study the (b) (4) which could be equally efficacious and may have improved tolerability compared to the 84 mg dose.

Sponsor Response: The Sponsor stated that (b) (4)

Division Comment: The Division stated that dose selection is the Sponsor's decision and that including a lower dose in Phase 3 is not a requirement.

7. Does the Agency concur with the primary endpoints of the study (the change from baseline to Week 12 in the number of incontinent episodes per week and in the average daily urinary frequency per week based on the entries in the 7-day Patient Urinary Diary)?

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Division Response: Yes. If two primary endpoints are used, both will need to achieve statistical significance at the 0.05 level over placebo to support drug approval. Alternatively, a single primary endpoint could be designated. Either change from baseline to week 12 in incontinence episode frequency or in average daily urinary frequency would be acceptable.

Sponsor's Response: The Sponsor stated that they will use incontinence episode frequency as the primary endpoint.

Sponsor Response: The Sponsor asked for clarification regarding the indication they will be able to pursue in labeling. In addition, the sponsor asked whether secondary endpoints, volume voided per micturition and micturition frequency, could be included in the product label.

Division Comment: Although it is premature to discuss labeling, the Division stated that the indication statement in the Sponsor's proposed labeling would be consistent with the triad symptomatology (incontinence, urgency, and frequency) currently approved for other overactive bladder products. The Division also clarified that the secondary endpoint, volume voided per micturition, could be included in the product label as it is for currently approved overactive bladder drug products.

8. Is it necessary to have the PVR urine volume as an exclusion criterion? If so, what volume does the Agency recommend should be used?

Division Response: Yes. The Division recommends that a PVR >200 mL be an exclusion criterion.

Sponsor Response: The Sponsor agreed and will modify the final protocol accordingly.

9. If PVR is necessary to include as a measurement for the Phase 3 trial, should both baseline and end-of-study measurements be performed?

Division Response: For safety considerations, both baseline and end-of-study post-void residual urine volume should be measured.

Sponsor Response: The Sponsor agreed and will modify the final protocol accordingly.

Additional Clinical Comments regarding the proposed Phase 3 trial:

A. Protocol Comments:

- 1) The sample patient urinary diary submitted will need to be modified before it is used in the trial.

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- i. **It is unclear how the exact number of voluntary micturitions and incontinence episodes experienced each day will be determined. The Division recommends that the time of each distinct voluntary void and incontinence episode be recorded.**
- ii. **How will stress incontinence episodes be distinguished from urge incontinence episodes in the patient urinary diary?**

Sponsor Response: The Sponsor agreed with the Division's recommendation and will modify the final diary accordingly to differentiate between stress and urge incontinence episodes.

- 2) **Please explain the rationale for recording the type and volume of fluid intake in the patient urinary diary.**

Sponsor Response: The Sponsor stated that they will not record type and volume of fluid intake in the patient urinary diary; they will modify the final diary accordingly.

- 3) **The drug application site should be specified. The protocol currently states that the application site is the abdomen or "other site as appropriate."**

Sponsor Response: The Sponsor asked if the Phase 3 protocol could be amended to include switches to multiple application sites.

Division Comment: The Division stated that, theoretically, this would be acceptable. However, in the absence of Phase 1 data that support bioequivalence of different application sites, the sponsor assumes the burden of providing adequate clinical safety and efficacy data to support approval of different sites. This could be a challenge. The sponsor has the option of employing a single application site (e.g., abdomen) throughout the conduct of the Phase 3 study/(ies) and conduct a Phase 1, multiple site application bioequivalence study that could be used to support multiple site applications in labeling. Results of this Phase 1 trial will be a review issue.

- 4) **Only patients taking potent CYP3A4 inhibitors should be excluded from the trial.**

Sponsor Response: The Sponsor agreed and will modify the final protocol accordingly.

- 5) **The Division does not anticipate allowing labeling claims (b) (4) (b) (4) If you believe that any of the (b) (4) (b) (4) to be used in the study are adequately validated (b) (4)**

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(b) (4) please submit the supporting documentation for review by the Division.

- 6) At least 50 subjects should complete 6 months of active treatment (12-week phase 3 trial plus 3 months open-label) to assess skin tolerability.

Sponsor Response: The Sponsor asked if it would be acceptable to lock their database at the end of active treatment, and then enroll the 3-month, open-label extension study.

Division Comment: The Division stated this would be acceptable if the Sponsor agrees to submit the data from the open-label extension study by the 120-day safety date for their NDA.

Sponsor Response: The Sponsor agreed.

B. Safety Comments:

- 1) A PSA should be measured at screening in all male subjects >40 years of age. Men with a PSA >4.0 ng/mL should be not be enrolled in the trial unless prostate cancer has been reasonably excluded.
- 2) A UTI should be recorded as an adverse event and treated accordingly in any subject with UTI symptoms and a positive urinalysis and urine culture, regardless of the colony count.

Sponsor Response: The Sponsor agreed and will modify the final protocol accordingly.

Pharmacokinetic Discipline

10. Is the proposed Phase 1 Site of Application pharmacokinetic study design sufficient to determine if application sites other than the abdomen are appropriate for the Phase 3 study?

Division Response: Yes, the proposed study design appears adequate.

11. Does the Agency have any additional comments on the Site of Application Study synopsis?

Division Response: Although not a requirement, we recommend that you characterize the systemic exposures of the R- and S-isomers of oxybutynin and desethyloxybutynin in this study, unless this information is already available for the gel formulation.

Sponsor Response: The Sponsor agreed.

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We recommend that the proposed site of application PK study should be completed prior to the initiation of the phase 3 clinical trial and the results of this study should support the use of application sites other than abdomen in phase 3.

Sponsor Response: The Sponsor agreed with the rationale for the recommendation. However, they stated that, at this time, if the results of the site of application PK study are not available by the time the Phase 3 study is initiated (4th quarter, 2006), they will proceed with the Phase 3 program as planned.

Additional Clinical Pharmacology Comments:

- 1. We recommend that you also investigate the (b) (4) of the gel in phase 3, along with the proposed 84 mg/day dose.**
- 2. You may consider including sparse sampling in phase 3 in order to explore covariates and exposure-response relationships.**
- 3. We recommend that you refer to the pre-IND meeting minutes (02-09-05) and address any pending clinical pharmacology issues including transfer potential, effect of bathing on systemic drug absorption, effect of washing on the residual drug on skin, PK interaction potential with sunscreen, etc.**

Sponsor Response: The Sponsor stated that they intend to address the above issues.

Pharmacology Discipline

- 12. Does the Agency concur that sufficient information and supporting materials have been provided to bring closure to the question pertaining to (b) (4) diethylene glycol monoethyl ether levels in the oxybutynin gel product?**

Division Response: No.

Because of information available on DGME at the (b) (4) concentration in a drug product (Dapsone Gel) approved for chronic use, no additional information is required for DGME in the oxybutynin gel product. Oral, dermal and photo carcinogenicity assays of Dapsone plus DGME (b) (4) were negative. DGME showed no reproductive toxicity in a battery of reproductive studies. Information for Dapsone gel is available on the FDA website.

Positive genotoxicity (chromosomal aberrations) and skin irritation have been reported with (b) (4) (although carcinogenicity was negative in oral studies in rats and mice). The Division is unable to locate reports of dermal

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carcinogenicity studies with (b) (4). Reviewable dermal carcinogenicity and phototoxicity data will be required with the NDA submission. Acceptable data could include animal and human literature references and manufacturers' Drug Master Files with reviewable data.

The Division is also unable to locate reviewable reproductive studies to support this indication. Please confirm and submit data supporting that systemic levels of (b) (4) do not significantly exceed endogenous levels. If this is not the case, reproductive studies will be needed before Phase 3.

Sponsor Response: The Sponsor agreed to submit a justification for (b) (4) content to support a request for a waiver of further reproductive studies. The Sponsor also agreed that they will add blood (b) (4) collections to the Phase 3 trial(s).

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/s/

George Benson

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