

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022504Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022504

SUPPL #

HFD # 580

Trade Name Axiron

Generic Name testosterone topical solution

Applicant Name Acrux Pharma Pty Ltd

Approval Date, If Known November 23, 2010

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.

N/A

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:

N/A

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?

N/A

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).

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:

MTE08

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"):

MTE08

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 # 070516 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: Jeannie Roule
Title: Regulatory Health Project Manager
Date: November 23, 2010

Name of Office/Division Director signing form: George Benson
Title: Deputy Director, 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/

JEANNIE M ROULE
11/23/2010

GEORGE S BENSON
11/23/2010

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 022504 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Axiron Established/Proper Name: testosterone topical solution Dosage Form: solution		Applicant: Acrux Pharmaceutical Agent for Applicant (if applicable): Kendle International
RPM: Jeannie Roule		Division: DRUP
<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)):</p> <p>No listed drugs were relied upon.</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input checked="" 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 checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 11/23/10</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>November 25, 2010</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
❖ 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 _____		<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 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <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 If yes, NDA # and date exclusivity expires:
<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>)	Action(s) and date(s) Approval, November 23, 2010
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. 	November 19, 2010
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

❖ 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 checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input 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. 	November 19, 2010
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Included
<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 	Included (Original and Final)
❖ 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>) 	Axiron-May 5, 2010 September 22, 2010
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA June 4, October 8, and November 19, 2010 <input checked="" type="checkbox"/> DRISK October 19, 2010 and October 26/10 <input checked="" type="checkbox"/> DDMAC October 15, 2010 <input checked="" type="checkbox"/> CSS June 11, 2010 <input checked="" type="checkbox"/> Other reviews SEALD November 19, 2010
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	April 9, 2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input type="checkbox"/> Not a (b)(2) November 15, 2010
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input type="checkbox"/> Not a (b)(2) November 23, 2010
❖ 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>) 	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ 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
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	February 2, 2010, April 9, 2010, May 5, 2010
❖ 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 type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg November 5, 2004 and August 31, 2009
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg March 13, 2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ 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 November 23, 2010
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None November 23, 2010
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	See CDTL Review
• Clinical review(s) (<i>indicate date for each review</i>)	March 17, 2010 and November 19, 2010
• 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>)	Included
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable June 11, 2010
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	October 19, 2010
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	November 18, 2010
• 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 type="checkbox"/> None October 19, 2010

⁵ Filing reviews should be filed with the discipline reviews.
Version: 8/25/10

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input checked="" type="checkbox"/> None requested
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None November 1, 2010 and Novmebr 19, 2010
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None November 1, 2010 and November 19, 2010
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None April 8, 2010 and November 1, 2010 and November 17, 2010 and November 22,2010
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None October 29, 2010
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None March 23, 2010 and September 22, 2010 and November 19, 2010
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<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(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 22, 2010 and November 19, 2010
❖ Microbiology Reviews <input checked="" 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 type="checkbox"/> Not needed March 4, 2010 and October 6, 2010
❖ 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</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	October 22, 2010
<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</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: November 4, 2010 <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</i>) (<i>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 checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input 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.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

JEANNIE M ROULE
11/24/2010

505(b)(2) ASSESSMENT

Application Information		
NDA # 022504	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Axiron Established/Proper Name: testosterone topical solution Dosage Form: solution Strengths: 2%		
Applicant: Acrux Pharm Pty. Ltd.		
Date of Receipt: January 25, 2010		
PDUFA Goal Date: November 25, 2010	Action Goal Date (if different): November 23, 2010	
Proposed Indication(s): Treatment of hypogonadism in men		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature	Non-Clinical Labeling

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor is relying upon the extensive body of literature that describes the potential toxicities of testosterone in nonclinical species and provided references that support the current language in Sections 8.1 and 13.1 of testosterone labels. The testosterone in this drug product is equivalent to the testosterone in the submitted references, and was evaluated at or above the proposed human doses.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If “YES”, please list which drug(s) and answer question d) i. below.
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If “NO” to (a) proceed to question #11.
If “YES” to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If **“YES”** to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If **“NO”**, proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

N020489 ANDRODERM (TESTOSTERONE FILM, EXTENDED RELEASE; TRANSDERMAL);
N021015 ANDROGEL (TESTOSTERONE GEL, METERED; TRANSDERMAL);
N021454 TESTIM (TESTOSTERONE GEL; TRANSDERMAL);
N021543 STRIANT (TESTOSTERONE TABLET, EXTENDED RELEASE; BUCCAL), and a generic pellet (implantation).

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]? YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt. YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

APPEARS THIS WAY ON ORIGINAL.

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

/s/

JEANNIE M ROULE
11/23/2010

MEMORANDUM

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

DATE: November 15, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: Comments concerning PI, Medguide, Carton and Container.

APPLICATION NUMBER: NDA 022504, Axiron

Various review teams had requested that comments and requests for information be sent to the Sponsor (see attached). Some issues were addressed and have been resolved. Some issues were addressed at a teleconference that took place between Acrux (the Sponsor), Lilly and FDA. Some issues have yet to be resolved but hope to be so that an action can take place on or before November 25, 2010

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, November 10, 2010 4:09 PM
To: 'wilson.michelle@kendle.com'
Subject: Carton

Michelle,

Please make the following changes to the carton:

AXIRON
(testosterone) topical solution*
30 mg per pump actuation
CIII (no change to this)

*Each pump actuation delivers 1.5 ml of solution

Multi-dose pump capable of dispensing 60 metered pump actuations.
For topical use only with enclosed applicator

No further changes.

Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, November 10, 2010 1:40 PM
To: 'wilson.michelle@kendle.com'
Subject: One change I know about

Michelle,

DMEPA has one final request for the carton and container. There might be one more from CMC but I will not know until 3 or 4 today. The label and Medguide should arrive around 4 or so today.
As currently presented, the "Rx Only" statement on the principle display panel appears in large, bolded font. Minimize and unbold this statement so it is less prominent than the established name and strength presentations

Thanks,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Thursday, November 11, 2010 4:05 PM
To: Roule, Jeannie
Subject: NDA 22-504: Axiron: Labeling Questions

Dear Jeannie,

Acrux would like to obtain feedback and discuss the following:

1-Information in section 12.3 (graph inserted)

In the November 2, submission of labeling, the Sponsor had proposed to retain the figure from MTE08 rather than include a modified version of a figure of total testosterone concentrations from MTE07 with a rationale for the same. However, the Agency's rationale for the figure remains unclear and the Sponsor wishes to gain clarity from the Agency regarding the objectives related to any figure represented in Section 12.3 to assist in mitigating the extent of further discussions.

2-The Sponsor wishes to understand the rationale for removal of the Day 15 data from Table 3 in section 14.1.

3-  (b) (4)

4-Regarding the Agency's comments on the name and number to call for reporting of adverse events, we wanted to clarify that while Acrux's name as the sponsor is listed as the point of contact, the number for reporting is a Lilly number as Lilly will be managing the safety database. With transfer of the NDA, Lilly intends to change the contact name on the USPI highlights section to Lilly and would like to gain agreement in a discussion on the transfer of the NDA that this could be done as a Changes Being Effected supplement vs. a Prior Approval Supplement.'

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

Reference ID: 2864567

11/16/2010

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Friday, November 12, 2010 10:21 AM
To: Roule, Jeannie
Subject: Re: Answer to some of your questions

Thanks!

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
Sent: 11/12/2010 10:16 AM EST
To: Michelle Wilson
Subject: Answer to some of your questions

Michelle,

Please see below:

-The Sponsor wishes to understand the rationale for removal of the Day 15 data from Table 3 in section 14.1.

Answer: While the overall study population did meet the primary endpoint at day 15, the US population did not. We do not believe this information should be included in this label.

[Redacted text block with (b) (4) label]

[Redacted text block]

=====

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Friday, November 12, 2010 10:37 AM
To: Roule, Jeannie
Subject: Re: One minor change

Thanks!

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
Sent: 11/12/2010 10:35 AM EST
To: Michelle Wilson
Subject: One minor change

Michelle,

One minor change:

8.1 Pregnancy

Pregnancy Category X [*See 'Contraindications' (4)*]. AXIRON is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Friday, November 12, 2010 11:08 AM
To: Roule, Jeannie
Subject: Re: Another one

Thanks!

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
Sent: 11/12/2010 10:59 AM EST
To: Michelle Wilson
Subject: Another one

Michelle,
Everyone is fine tuning everything. Sorry.
The carton and container should state:

(b) (4)

Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: Roule, Jeannie
Sent: Monday, November 15, 2010 1:20 PM
To: 'wilson.michelle@kendle.com'
Subject: One more response

Michelle,

This is the response to a question posed last week:

With transfer of the NDA, Lilly intends to change the contact name on the USPI highlights section to Lilly and would like to gain agreement in a discussion on the transfer of the NDA that this could be done as a Changes Being Effected supplement vs. a Prior Approval Supplement.'

FDA response:

Any changes to a REMS is considered a REMS modifications. All REMS modifications must be submitted as prior approval supplement and not a CBE.

All REMS modifications will have a 6 month clock.

Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: Roule, Jeannie
Sent: Tuesday, November 16, 2010 9:22 AM
To: 'wilson.michelle@kendle.com'
Subject: RE: NDA 22-504: Request for Clarification: Order of °C vs °F

Michelle,

It should be consistent with the way USP prescribes.

So the carton/container, label and Medguide should be revised accordingly.

Jeannie

From: wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]
Sent: Tuesday, November 16, 2010 4:47 AM
To: Roule, Jeannie
Subject: Re: NDA 22-504: Request for Clarification: Order of °C vs °F

Hi Jeannie,

Just one additional question - should all the documents (including the Med Guide) be consistent with the USP?

Thank you very much.

Best wishes,

Michelle

From: Michelle Wilson/CIN/Kendle
To: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
Date: 11/15/2010 08:00 PM
Subject: NDA 22-504: Request for Clarification: Order of °C vs °F

Dear Jeannie,

We would appreciate some clarification regarding the order of °C vs °F (see below).

PI – Storage conditions

USP Controlled Room Temperature: Store at 25°C (77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F) – this was in the FDA marked up label received 11Nov 2010 & is consistent with the requirements of the USP but is not consistent with the request below. Acrux would appreciate confirmation that this is correct.

Carton submitted 12 Nov 2010 -

(b) (4)

Thank you very much!

Best wishes,

Michelle

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
Sent: 11/12/2010 10:37 AM EST
To: Michelle Wilson

Reference ID: 2864567

11/16/2010

Subject: Carton and container

Michelle,

I apologize but I am going to send each change as I receive them.

The PI temperature storage statement with the revisions will state F followed by C for the US market. However, the storage statement should be the same on the carton and container.

Thanks,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108; Mobile (513) 578-5671 (NEW) |
Fax (513) 763-7628

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Tuesday, November 16, 2010 9:31 AM
To: Roule, Jeannie
Subject: RE: NDA 22-504: Request for Clarification: Order of °C vs °F

Jeannie,

Thank you very much!

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108; Mobile (513) 578-5671 (NEW) |
Fax (513) 763-7628

From: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
To: "wilson.michelle@kendle.com" <wilson.michelle@kendle.com>
Date: 11/16/2010 09:22 AM
Subject: RE: NDA 22-504: Request for Clarification: Order of °C vs °F

Michelle,

It should be consistent with the way USP prescribes.

So the carton/container, label and Medguide should be revised accordingly.

Jeannie

From: wilson.michelle@kendle.com [<mailto:wilson.michelle@kendle.com>]
Sent: Tuesday, November 16, 2010 4:47 AM
To: Roule, Jeannie
Subject: Re: NDA 22-504: Request for Clarification: Order of °C vs °F

Hi Jeannie,

Just one additional question - should all the documents (including the Med Guide) be consistent with the USP?

Thank you very much.

Best wishes,

Michelle

From: Michelle Wilson/CIN/Kendle
To: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
Date: 11/15/2010 08:00 PM
Subject: NDA 22-504: Request for Clarification: Order of °C vs °F

Reference ID: 2864567

11/16/2010

Dear Jeannie,

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PI – Storage conditions

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Carton submitted 12 Nov 2010 -

(b) (4)

(b) (4)

Thank you very much!

Best wishes,

Michelle

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
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Subject: Carton and container

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Thanks,
Jeannie

Jeannie Roule
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Fax (513) 763-7628

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/s/

JEANNIE M ROULE
11/16/2010

MEMORANDUM

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

DATE: October 27, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: Request from CMC reviewer regarding the carton and container

APPLICATION NUMBER: NDA 022504, Axiron

The CMC Reviewer requested that the following comments be sent to the Applicant.
Please see attached email correspondences.

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, October 27, 2010 2:21 PM
To: 'wilson.michelle@kendle.com'
Subject: CMC and name

Michelle,

It has been decided. Please see the following comments:

1. Please modify the presentation of proprietary name, established name and strength of the drug product on the immediate container and carton labels as shown below and submit the revised labels.

Axiron®
(testosterone) topical solution
2%

2. The proprietary name, established name and strength of the drug product on the PI should also be changed as following.

Axiron® (testosterone) topical solution 2%

Please make the appropriate changes on your PI and carton and container. Send us a new carton and container as soon as possible.

Thanks,
Jeannie

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
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Email: jeannie.roule@fda.hhs.gov

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/s/

JEANNIE M ROULE
10/27/2010

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/s/

REBECCA A MCKNIGHT
10/25/2010

MEMORANDUM

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

DATE: October 22, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: DRISK comments. Recommendations and edits for REMS

APPLICATION NUMBER: NDA 022504, Axiron

The attached information was emailed to the Applicant on October 22, 2010. It includes all of the comments and recommendations for the Applicant's REMS from the DRISK reviewer. Please see attached email correspondences.

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Friday, October 22, 2010 2:37 PM
To: Roule, Jeannie
Subject: Re: NDA 22504

Jeannie,

Thank you very much! Have a great weekend!

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

From: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
To: "wilson.michelle@kendle.com" <wilson.michelle@kendle.com>
Date: 10/22/2010 01:31 PM
Subject: NDA 22504

Michelle,

I have attached a document that contains the REMS review. There are many comments but the actual REMS document will take very little time to correct.

Please keep in mind that the review of the Medguide has not been completed.

I am hoping to send the label and Medguide on Monday or Tuesday of next week. Hopefully there will be a quick turn-around. After you make your changes, please email the newest version to me. Once we agree, I will have you send the final version to your NDA (as a formal submission). Let me know if you have any questions.

Regards,
Jeannie

Jeannie Roule
Regulatory Project Manager

10/25/2010

Division of Reproductive and Urologic Products
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Food and Drug Administration
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Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

[attachment "REMS comments sent to Sponsor Oct 22.doc" deleted by Michelle Wilson/CIN/Kendle]

DRISK has completed their review of your proposed REMS and we have the following comments and recommendations:

See the appended AXIRON REMS proposal (Appendix A of this memo) for track changes corresponding to comments in this review.

a. **GOAL**

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of AXIRON (testosterone).

b. Your Medication Guide distribution plan appears to be acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.

- We remind you that under 21 CFR 208.24, you are responsible for ensuring that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. You state that a Medication Guide will be available in each carton of AXIRON (testosterone) Solution. We find your unit-of use distribution plan acceptable.
- We acknowledge that you will include an instruction on the AXIRON (testosterone) container or package label alerting the pharmacist to provide the Medication Guide to each person when the drug is dispensed.
- See our editorial comments on this section of the proposed REMS (see Appendix C).

c. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

d. Regarding your REMS Assessment Plan

1. The submitted methodology lacks sufficient detail to complete a review. We will defer comment of your proposed assessment until you have submitted a full protocol and survey instrument.
2. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Axiron. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Axiron.

3. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.

If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

4. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
5. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
6. Ensure the sample is demographically representative of the population who use the drug (patients).
7. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
8. List the inclusion criteria. For example, eligible patient respondents must be:
 - Age 18 or older
 - Currently taking Axiron or have taken the drug in the past 3 months
 - Not currently participating in a clinical trial involving Axiron
 - Not a healthcare provider

Submit any screener instruments, and describe any quotas of sub-populations used.

9. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.
10. Explain how you control for limitations or bias associated with the methodology and survey instrument(s).

11. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to receive or take (patients) the drug, and that their answers and personal information will be kept confidential and anonymous.

12. Clarify in your methodology that respondents are eligible for one wave of the survey only.
13. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

14. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

15. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Axiron?" section of the Medication Guide.

Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

16. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

Do not allow respondents the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

17. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

18. Prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Axiron. The Medication Guide is a paper handout that contains important information about the risks associated with use of Axiron and how to use Axiron safely. Medication Guides always include the title "Medication Guide" followed by the word Axiron and its pronunciation. The Medication Guide usually has sections titled "What is the most important information I should know about Axiron," "What is Axiron," and "Who should not take Axiron."

19. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

Who gave you the Medication Guide for Axiron? (Select all that apply)

- a) My doctor or someone in my doctor's office
- b) My pharmacist or someone at the pharmacy
- c) Someone else - please explain:

d) I did not get a Medication Guide for Axiron

Did you read the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did you understand what you read in the Medication Guide?

- a) All,
- b) Most,
- c) Some,
- d) None

Did someone offer to explain to you the information in the Medication Guide?

- a) Yes, my doctor or someone in my doctor's office
- b) Yes, my pharmacist or someone at the pharmacy

c) Yes, someone else -- please explain:

d) No

Did you accept the offer? Yes or No

Did you understand the explanation that was given to you?

a) All,

b) Most,

c) Some,

d) None

Did or do you have any questions about the Medication Guide?
Yes or No (If Yes, list your question(s) below) Note:
Group/code this open text field prior to submitting to FDA

20. Analyze results on an item-by-item or variable-by-variable basis.

You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables). You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

2 Pages of Draft Labeling have been Withheld in Full
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/s/

JEANNIE M ROULE
10/25/2010

MEMORANDUM

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

DATE: October 14, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: DMEPA request for changes to carton and container

APPLICATION NUMBER: NDA 022504, Axiron

The DMEPA Reviewer requested that the following comments be sent to the Applicant.
Please see attached email correspondences.

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Thursday, October 14, 2010 12:53 PM
To: Roule, Jeannie
Subject: Re: NDA 22504 Axiron

H Jeannie,

Receipt confirmed!

Best wishes,

Michelle

From: "Roule, Jeannie" [Jeannie.Roule@fda.hhs.gov]
Sent: 10/14/2010 12:35 PM AST
To: Michelle Wilson
Subject: NDA 22504 Axiron

Michelle,

DMEPA has more comments for your current carton. I might have a few more form CMC later today. Please confirm receipt

Jeannie

A. GENERAL COMMENTS FOR LABELS AND LABELING (2%)

1. The graphic symbol above the proprietary name presentation is too large, distracts from the proprietary name, and competes with its prominence. Reduce the size of this symbol.
2. The established name still appears to be presented in a font that is too thin. In accordance with 21 CFR 201.10(g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
3. In order to improve clarity and minimize confusion, revise the multi-dose pump statement on the principle display panel to read as follows: *Multi-dose pump capable of dispensing 60 metered pump actuations. One full pump actuation delivers 30 mg of Axiron.* Additionally, remove the statement from the rear panel of the container label and the side panel of the carton labeling that (b) (4)
4. Remove the statement (b) (4)
(b) (4) Patients should be receiving dosage instructions from their providers and not from the Medication Guide. Additionally, there is already a statement stating "See package insert for full prescribing information." Alternatively, the statement can be revised to state *See accompanying Medication Guide for application instructions*
5. Remove the orange color boxing around the "Rx Only" statement. As currently presented, the color boxing makes the "Rx Only" statement more prominent than the established name

10/14/2010

and strength presentation. Color boxing is typically used to highlight and bring prominence to important information. Therefore, as currently proposed, the orange color boxing is inappropriately applied.

6. It is currently unclear what the purple color strip at the bottom of the principle display panel is for. As currently presented, it is distracting and does not appear to serve any purpose. Remove this color strip.

B. RETAIL CARTON LABELING (2%)

1. The light gray colored graphic on the side panel is distracting and interferes with the presentation of the proprietary name, established name, and strength on that panel. Remove this colored graphic.

2. It is currently unclear what the empty box outline on the side panel is for. As currently presented, it does not appear to serve any purpose. Please clarify its purpose, otherwise remove the box.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
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Direct Line: (301) 796-3993
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Email: jeannie.roule@fda.hhs.gov

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/s/

JEANNIE M ROULE
10/14/2010

MEMORANDUM

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

DATE: September 16, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: Clinical Pharmacology request for information

APPLICATION NUMBER: NDA 022504, Axiron

The Clinical Pharmacology Reviewer requested that the following requests for information be sent to the Applicant.

Please see attached email correspondences.

Roule, Jeannie

From: Roule, Jeannie
Sent: Tuesday, September 14, 2010 12:07 PM
To: 'wilson.michelle@kendle.com'
Subject: Request for information NDA 22504

Michelle,

Below are the requests from the Clinical Pharmacology reviewer. Please respond as soon as possible and let me know if you have any further questions.

Regards,
Jeannie

1. In your response dated May 12, 2010 to the Division's 74-day letter dated April 9, 2010 (i.e., response to Division's Question 3a), you have acknowledged that the effect of the body mass index (BMI) on systemic testosterone exposure will be a review issue. However, there was no additional information submitted. During our review, it was found that the efficacy and safety of Axiron was only assessed in study subjects with BMI < 35 kg/m². We request that you submit your justification or any information that will address the potential effect of the body mass index (BMI) on systemic testosterone exposure in the population with BMI > 35 kg/m². In addition, we request that you conduct a correlation analysis with the data you have obtained in Studies MTE08 and MTE09 (but not limited to) and submit your rationale/conclusion addressing the potential of the body mass index (BMI) effect on systemic testosterone exposure

2. In your responses dated May 12, 2010 to the Division's 74-day letter dated April 9, 2010 (i.e., response to Division's Question 3b), you state that testosterone blood levels of subjects had reached steady-state after 7 days of treatment in Studies MTE05 and MTE07. During our review, it was noted that Study MTE05 was conducted using a different formulation (i.e., 1% testosterone) while Study MTE07 was conducted with both the 1% and 2% testosterone (i.e., to-be-marketed [TBM] formulation). Furthermore, it was noted that the Study Report of MTE07 states that "For the assessment of steady state, the mean difference between total testosterone levels at pre-dose and at 24 hours post-dose on Day 7 was 76 ng/dL, which was statistically significant (p = 0.001). This difference did not depend significantly on period, but was similar across treatments. This could either indicate that steady state was not achieved within 7 days of dosing...". We request that you submit your rationale of concluding that the steady-state of testosterone was reached following 7 days of treatment with the TBM formulation.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
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Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Tuesday, September 14, 2010 2:00 PM
To: Roule, Jeannie
Subject: Re: Request for information NDA 22504

Thanks, Jeannie!

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

From: "Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>
To: "wilson.michelle@kendle.com" <wilson.michelle@kendle.com>
Date: 09/14/2010 12:07 PM
Subject: Request for information NDA 22504

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Regards,
Jeannie

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9/16/2010

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Jeannie Roule
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Center for Drug Evaluation and Research
Food and Drug Administration
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Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Thursday, September 16, 2010 5:20 AM
To: Roule, Jeannie
Subject: NDA 22-504, Updates on Timing

Dear Jeannie,

As we discussed yesterday, we had an Acrux team meeting last evening and discussed the timing of the MTE12 CSR and the recent requests from the clinical pharmacology reviewer. As requested, I've summarized the timing for both items below. Please let me know if you have any questions.

A) With respect the MTE12, Acrux Pharma commits to providing the following to the FDA:

1. A Synopsis in Word format via e-mail, containing a descriptive summary of the PK data and safety data, summary Table(s) and Figure(s), as well as overall study conclusions, by **30 September 2010**
2. A full Clinical Study Report, in Word format via e-mail, containing a PK report including statistical analysis, Tables, Listings and Figures, and overall study conclusions, by **7 October 2010**
3. A full Clinical Study Report as above, but published to NDA 22-504 by **14 October 2010**

B) With respect to the questions from the Clinical Pharmacology reviewer, we will provide a detailed response to the FDA on Tuesday **21 September 2010**

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

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/s/

JEANNIE M ROULE

09/16/2010

MEMORANDUM

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

DATE: August 3, 2010

TO: Acrux Pharmaceuticals

FROM: Division of Reproductive and Urologic Products, Jeannie Roule

SUBJECT: CMC comments

APPLICATION/DRUG: NDA 22504, Axiron

The Applicant had emailed a few comments and questions for the CMC review team. The Applicant thought that a teleconference might be required to resolve some issues. The CMC reviewer was able to answer the Applicant's questions and a teleconference was deemed unnecessary. See attached emails.

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Wednesday, August 04, 2010 5:42 AM
To: Roule, Jeannie
Subject: RE: Axiron NDA 22-505: Request for CMC Tcon

Dear Jeannie,

Acrux wishes to thank the CMC reviewer for providing a response to our questions & the offer to entertain a teleconference. We feel that the questions have been adequately addressed and that a teleconference will not be necessary.

Further, we wish to communicate our intention to submit the following documentation to assist in the determination of the expiration dating period.

1. 15 month 25°C stability data on the registration batches - appearance and content and impurity data.
2. Additional supportive stability data for registration batch units stored at 30°C for 6 months
3. A final report on the colour investigation that will include data obtained from the supplier investigation.

Acrux will provide all reports as soon as they become available. All information will be provided by September 3.

We trust that this acceptable.

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
 Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108; Mobile (513) 578-5671 (NEW) |
 Fax (513) 763-7628

"Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>

To <wilson.michelle@kendle.com>

cc

08/03/2010 02:37 PM

Subject RE: Axiron NDA 22-505: Request for CMC Tcon

Michelle,

Please read these responses. If Acrux is satisfied with the answers, there is no need for a teleconference. If you still want a tcon, the only time available this week is Thursday but not until after 11:00 am. Please let me know what Acrux thinks.

Regards,
 Jeannie

Question #1 Anything submitted prior to August 25th would not extend the clock. We would be okay with submitting information by September 3 without CMC requiring a clock extension (it's only an additional week) in order to have the content and impurity data to help in our decision making.

Question #2 The information in SN0004 and SN0007 is acceptable, but we need the content and impurity information before we can decide on whether we will be able to use the supportive data for determination of the expiration dating period.

From: wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]
Sent: Tuesday, August 03, 2010 4:48 AM
To: Roule, Jeannie
Subject: Axiron NDA 22-505: Request for CMC Tcon

8/4/2010

Dear Jeannie,

As we discussed, Acrux would like to talk with the CMC reviewer, hopefully sometime this week. Acrux has provided some background information and questions for discussion below. Please let me know when the Tcon could occur. Early morning (8 AM) or late afternoon (as late as possible) Tcon times work best for Acrux.

Thank you very much.

Best wishes,

Michelle

Background Information and Update

*The root cause of the pale red colour is confirmed to be the batch of povidone used by Orion Corporation

*Significant analytical work has been undertaken which includes concentration of the samples via extraction. Due to the trace levels of the colour-forming species present, identification by chromatographic and spectroscopic analyses have not been conclusive to date, but work is still in progress.

*We are in communication with the supplier of the povidone raw material (b) (4) and they are also conducting their own internal investigation. We are expecting a report from (b) (4) by Mid-Late August.

* Due to the trace amounts of the impurity present, Acrux still considers that it is unlikely that the levels of this impurity will have an impact on the safety and efficacy of the Axiron formulation.

Acrux plans to perform a 15 month time point Appearance test on the Registration batches with testing to be completed by 19 Aug 2010. Data can be provided to the FDA by 23 Aug 2010.

Questions for Tcon

1. What is the latest date that we can provide data so as to not affect the PDUFA date? Given that there has been a lot of data generated it would take some time to collate this as a report. How much information do the CMC reviewers require to complete their review & what would be the easiest way to communicate the data? In addition, we are hoping to test samples at 15 months to evaluate the appearance (red coloration). We anticipate having data available by 18th August. If content & impurity data was required, this could be available by end August.

2. What data will the FDA be using to establish product shelf life? During the CMC telecon held on the 17th March, the FDA stated that if the product stored under accelerated conditions had the pink color and the product stored under 'real time' conditions (25 °C) did not, then the FDA would use only the real time stability data to support expiry dating. In the 74 day letter the question posed was: "Be aware that our evaluation of the red color and oily droplets observed in your registration stability samples will have a direct impact on the expiration dating period. Supporting stability data gathered on the Phase 3 clinical supplies may not be used to set the expiration dating period if the quality of the drug product manufactured at the proposed commercial facility cannot be assured". We have since responded in SN0004 & SN0007 with additional information. Is this acceptable to the FDA & are they accepting historical data when evaluating shelf life?

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
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Fax (513) 763-7628

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
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/s/

JEANNIE M ROULE

08/05/2010

MEMORANDUM

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

DATE: June 30, 2010

TO: Acrux Pharmaceuticals

FROM: Division of Reproductive and Urologic Products, Jeannie Roule

SUBJECT: Tcon

APPLICATION/DRUG: NDA 22504, Axiron

We had a teleconference with the Applicant and asked them to conduct another transfer study using the 2% solution. The Applicant agreed and will send in a protocol for the study. See attached emails.

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, June 30, 2010 8:56 AM
To: 'wilson.michelle@kendle.com'
Subject: RE: Acrux Tcon Confirmation

(b) (4)



From: wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]
Sent: Tuesday, June 29, 2010 4:48 AM
To: Roule, Jeannie
Subject: Acrux Tcon Confirmation

Hi Jeannie,

Acrux has confirmed that the Tcon proposed for 30 June at 3:30 PM is acceptable to them. As we discussed, we'll await the call-in number.

Thank you very much.

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

Roule, Jeannie

From: Yu, Chongwoo
Sent: Monday, June 28, 2010 11:54 AM
To: Roule, Jeannie
Cc: Kaul, Suresh; Kim, Myong-Jin; Apparaju, Sandhya; McNellis, Donald
Subject: NDA 22504 Axiron Clin Pharm Comments for the Sponsor

Importance: High

As discussed this morning, pls find Clin Pharm's comments for the Sponsor below:

Comment for the Sponsor:

As communicated to you via the 74 day letter dated April 9, 2010, the potential for secondary exposure of testosterone to women and children is still a concern. While an interpersonal transfer study was conducted with a 1% formulation, it is unclear whether the T-shirt barrier will prevent the transfer of testosterone with the to-be-marketed formulation (i.e., 2% formulation) to the same extent. Considering the wide application area around the axilla and the Agency's awareness regarding the interpersonal transfer potential from transdermal testosterone formulations, we request that you address this by preferably conducting a clinical study evaluating interpersonal transfer potential with the to-be-marketed 2% testosterone formulation or submitting available information (e.g., literature and/or unsubmitted data) that can address this concern.

Pls let me know if you have any questions. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

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/s/

JEANNIE M ROULE

08/05/2010

MEMORANDUM

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

DATE: July 21, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: Clinical Pharmacology comment

APPLICATION NUMBER: NDA 022504, Axiron

Clinical Pharmacology requested that the following comment be sent to the Applicant.

Roule, Jeannie

From: Roule, Jeannie
Sent: Wednesday, July 21, 2010 3:34 PM
To: 'wilson.michelle@kendle.com'
Subject: Protocol

Michelle,

We have one more comment for your protocol. There is a possibility of a few more.

Concerning your study MTE12:

Please confirm that the instructions being given to the male study subjects regarding the application of Axiron is the same as the instructions that will be given to patients in labeling.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: Yu, Chongwoo
Sent: Wednesday, July 21, 2010 3:24 PM
To: Roule, Jeannie
Cc: Kaul, Suresh; Kim, Myong-Jin; McNellis, Donald
Subject: RE: An additional comment for Acrux re MTE12

As discussed earlier in person today, I concur with the Don's comment.
Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: McNellis, Donald
Sent: Wednesday, July 21, 2010 2:53 PM
To: Roule, Jeannie
Cc: Yu, Chongwoo; Kaul, Suresh; Kim, Myong-Jin
Subject: An additional comment for Acrux re MTE12

Jeannie

We would like to send an additional comment to Acrux concerning their study MTE12:

Please confirm that the instructions being given to the male study subjects regarding the application of Axiron is the same as the instructions that will be given to patients in labeling.

Please check with Chongwoo for any changes or additions he may have before sending it.

Thanks

Don

=====
*Donald McNellis, MD
Medical Officer
Division of Reproductive and Urological Products
Center for Drug Evaluation & Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
301-796-0328*

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Friday, July 23, 2010 9:24 AM
To: Roule, Jeannie
Subject: Re: Protocol: MTE12: NDA 22-504

Dear Jeannie,

The MTE12 protocol has already been submitted to local ethics committee for approval in order to meet the study report submission timelines agreed to with the FDA.

Acrux Pharma confirms that the study drug (testosterone 2% solution) will be applied to the male subjects consistent with that described in the proposed label. In particular, the MTE12 protocol requires that the study drug be applied to an acceptable application area as shown by Figure 1 in the protocol and we confirm that this corresponds exactly to the diagram of the acceptable application area as included in the proposed draft label.

We wish to highlight that the study drug will be applied to the male subjects by a study nurse, rather than by the subject themselves. The rationale being that with a limited sample size (n=10) and with only a single dose application, this approach may limit inter-subject variability. This approach is also consistent with the application method as used in the most recent single-dose washing study (MTE11) conducted in January 2010.

Please could the FDA confirm that this is acceptable.

Thank you very much!

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

"Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>

To <wilson.michelle@kendle.com>

cc

Subject Protocol

07/21/2010 03:34 PM

Michelle,

7/28/2010

We have one more comment for your protocol. There is a possibility of a few more.

Concerning your study MTE12:

Please confirm that the instructions being given to the male study subjects regarding the application of Axiron is the same as the instructions that will be given to patients in labeling.

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: Yu, Chongwoo
Sent: Friday, July 23, 2010 4:40 PM
To: Roule, Jeannie
Cc: Kim, Myong-Jin
Subject: RE: An additional comment for Acrux re MTE12

Thanks for reminding us.
Yes, we do not have any additional comments at this moment.

BTW, is the Sponsor going to submit their final protocol once they receive DRUP's comments?
Just wondering since you mentioned it in your email below.
Thanks and have a great weekend!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
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Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Roule, Jeannie
Sent: Friday, July 23, 2010 11:43 AM
To: Yu, Chongwoo
Subject: RE: An additional comment for Acrux re MTE12

Chongwoo,

The Sponsor emailed me this (see below) today with this last bit of information. I thought it help with your discussion. I will wait for your final comments and then the Sponsor will be able to submit their final protocol.

Regards,
Jeannie

The drug will be applied to the male subjects consistent with that described in the proposed label. In particular, the MTE12 protocol requires that the study drug be applied to an acceptable application area as shown by Figure 1 in the protocol and we confirm that this corresponds exactly to the diagram of the acceptable application area as included in the proposed draft label.

We wish to highlight that the study drug will be applied to the male subjects by a study nurse, rather than by the subject themselves. The rationale being that with a limited sample size (n=10) and with only a single dose application, this approach may limit inter-subject variability. This approach is also consistent with the application method as used in the most recent single-dose washing study (MTE11) conducted in January 2010.

From: Yu, Chongwoo
Sent: Friday, July 23, 2010 11:39 AM
To: Roule, Jeannie
Subject: RE: An additional comment for Acrux re MTE12

We are under discussion, I will get back to you once our discussion is finalized. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
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10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Roule, Jeannie
Sent: Friday, July 23, 2010 8:40 AM
To: Yu, Chongwoo
Subject: RE: An additional comment for Acrux re MTE12

Chongwoo,

Do you know if MJ will have any further comments for Acrux concerning their transfer study for Axiron?

Thanks and I hope you have a pleasant weekend.

Regards,
Jeannie

From: Yu, Chongwoo
Sent: Wednesday, July 21, 2010 4:09 PM
To: Roule, Jeannie
Cc: Kaul, Suresh; Kim, Myong-Jin; McNellis, Donald
Subject: RE: An additional comment for Acrux re MTE12

To elaborate why we are asking for this confirmation, pls see below:

There are 2 different diagrams/pictures on pages 21 and 22 of the most recently conducted MTE11 clinical study report, one called as the acceptable wiping area and the other called acceptable application area which looks quite different from each other.

We would like to the Sponsor to confirm that the acceptable application area was consistent through out the clinical development program including the Phase 3 trials, MTE08 and 09.

Hope this helps. Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
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10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: Yu, Chongwoo

Sent: Wednesday, July 21, 2010 3:24 PM
To: Roule, Jeannie
Cc: Kaul, Suresh; Kim, Myong-Jin; McNellis, Donald
Subject: RE: An additional comment for Acrux re MTE12

As discussed earlier in person today, I concur with the Don's comment.
Thanks!

- Chongwoo

Chongwoo Yu, Ph.D.
Office of Clinical Pharmacology - DCP 3
U.S. Food and Drug Administration - CDER/OTS
10903 New Hampshire Ave., Bldg 51 Room 3153
Silver Spring, MD 20993-0002

Phone: +1-301-796-2335
Fax: +1-301-847-8719
Email: chongwoo.yu@fda.hhs.gov

From: McNellis, Donald
Sent: Wednesday, July 21, 2010 2:53 PM
To: Roule, Jeannie
Cc: Yu, Chongwoo; Kaul, Suresh; Kim, Myong-Jin
Subject: An additional comment for Acrux re MTE12

Jeannie

We would like to send an additional comment to Acrux concerning their study MTE12:

Please confirm that the instructions being given to the male study subjects regarding the application of Axiron is the same as the instructions that will be given to patients in labeling.

Please check with Chongwoo for any changes or additions he may have before sending it.

Thanks

Don

=====
*Donald McNellis, MD
Medical Officer
Division of Reproductive and Urological Products
Center for Drug Evaluation & Research
10903 New Hampshire Avenue
Silver Spring, MD 20993
301-796-0328*

Application
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Submitter Name

Product Name

NDA-22504

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JEANNIE M ROULE

08/05/2010

MEMORANDUM

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

DATE: July 15, 2010

TO: NDA 022504

THROUGH : Jeannie Roule

SUBJECT: Container/Carton label comments

APPLICATION NUMBER: NDA 022504, Axiron

CMC and DMEPA requested that the following comments be sent to the Applicant (see attached). As soon as the Applicant makes the appropriate revisions and there is agreement between the Applicant and DRUP, the Applicant will submit a formal submission via edr.

Roule, Jeannie

From: Roule, Jeannie
Sent: Thursday, July 15, 2010 3:28 PM
To: 'wilson.michelle@kendle.com'
Subject: Carton/Container NDA 22504

Attachments: Comments to Acrux Carton and Container July.doc

Dear Michelle,

Attached is a word document containing a list of comments concerning your container/carton label for NDA 22504, Axiron. We request a prompt written response in order to continue our evaluation of your NDA. Kindly acknowledge receipt of this email.

If you have any questions, please call or email me.

Regards,
Jeannie



Comments to
rux Carton and C

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

Roule, Jeannie

From: wilson.michelle@kendle.com
Sent: Thursday, July 15, 2010 3:30 PM
To: Roule, Jeannie
Subject: Re: Carton/Container NDA 22504
Attachments: Comments to Acrux Carton and Container July.doc

Dear Jeannie,

Thank you very much. I will pass this on to Acrux.

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

"Roule, Jeannie" <Jeannie.Roule@fda.hhs.gov>

To <wilson.michelle@kendle.com>

cc

Subject: Carton/Container NDA 22504

07/15/2010 03:27 PM

Dear Michelle,

Attached is a word document containing a list of comments concerning your container/carton label for NDA 22504, Axiron. We request a prompt written response in order to continue our evaluation of your NDA. Kindly acknowledge receipt of this email.

If you have any questions, please call or email me.

Regards,
Jeannie

<<Comments to Acrux Carton and Container July.doc>>

Jeannie Roule

7/28/2010

We are reviewing the container/carton label section of your submission and have the following comments and information requests. Other comments may follow at a later date. We request a prompt written response in order to continue our evaluation of your NDA.

1. The established name should be changed to “(testosterone) solution 2%” on all container/carton labels and the package insert as recommended during the preNDA meeting held on 31-Aug-2009.
2. Include the appropriate NDC number on all container/carton labels and the package insert.
3. Print expiration date per 21 CFR 201.17 and lot number per CFR 201.18 on the container label and carton labeling, preferably not on the principle display panel to minimize crowding.
4. All prescription drug products are required to have a bar code printed on the immediate container/carton labels per 21 CFR 201.25. Please print bar codes on the immediate container/carton labels.
5. Print “See package insert for full prescribing information” (b) (4)
 (b) (4)
6. We recognize the bottle is unit-of-use for this product, and we are concerned that children may inadvertently access these bottles. Consider using a child-resistant closure to prevent accidental exposure.
7. The blue font utilized on top of a blue background color is difficult to read. Change the font color and/or background color to ensure improved contrast and readability of the container label and carton labeling.
8. The established name appears in a thin font that is difficult to read. In accordance with 21 CFR 201.10(g)(2), ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
9. The graphic symbol embedded into the proprietary name presentation distracts from the proprietary name and competes with its prominence. Additionally, under 21 CFR 201.15 (a)(6), this symbol may be considered an “obscuring design.” Remove the graphic symbol.
10. The strength designation is not adequately prominent. Increase the prominence of the product strength on the container label and carton labeling.

11. In order to ensure the correct route of administration is utilized, bold the statement “For topical use only”, and move it to the principle display panel. Expand this statement to read “For topical use only with enclosed applicator” to ensure patients do not utilize other devices for administration of this product.
12. Per 21 CFR 201.10(d)(1), add a statement informing healthcare providers of the actual amount of testosterone delivered for each specified measure of the drug, such as *1 pump actuation of Axiron delivers 30 mg of testosterone.*
13. The dosing table does not convey the necessary dosing instructions for this product to ensure appropriate use. Revise the dosing table to reflect the prescribed dose in milligrams within the “Prescribed Daily Dose” column. This table should also reflect the number of application sites required for each dose of Axiron. In reformatting this table, keep in mind that information must be presented in a manner that is easily legible without crowding the panel and/or obscuring other important information. Alternatively, if adequate space is not available, eliminate the dosing table and refer the user to the package insert for complete dosing information.
14. Minimize the distributor’s logo. As currently presented, this information is more prominent than that of the proprietary name and established name due to its coloring and size.
15. The curved line graphic utilized on the background of the container label and carton labeling interferes with the readability of information. Remove the graphic and consider utilizing one solid background color for the container label and carton labeling.
16. A medication guide is required for this product; therefore, ensure that the following statement is clearly displayed in bold font on the principle display panel: “Dispense the enclosed Medication Guide to each patient.”

Application
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Product Name

NDA-22504

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/s/

JEANNIE M ROULE

08/05/2010

MEMORANDUM

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

DATE: July 21, 2010

TO: IND 70516

THROUGH : Jeannie Roule

SUBJECT: Draft MTE012 protocol entitled, "A phase I study to evaluate the potential for interpersonal transfer of testosterone following single dose application of 2% Testosterone Metered Dose (MD)-Lotion®." received from Acrux Pharmaceutical on July 13, 2010

APPLICATION/DRUG: IND 70516 and NDA 22504, Axiron

Acrux requested comments on the above stated protocol. Originally it was sent via email but it was also submitted officially to their IND 70516. Our response was sent to Acrux via email. See attached documents.

Roule, Jeannie

From: Roule, Jeannie
Sent: Monday, July 12, 2010 3:46 PM
To: 'wilson.michelle@kendle.com'
Subject: RE: Acrux IND 70,516: MTE012 protocol_V1.0_12July10.doc

Michelle,

Thanks. I will forward this to the MO. Please submit it formally as well so we have a documented record of it.

Jeannie

From: wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]
Sent: Monday, July 12, 2010 3:41 PM
To: Roule, Jeannie
Subject: Acrux IND 70,516: MTE012 protocol_V1.0_12July10.doc

Dear Jeannie,

As we discussed, I've attached the Word version of the draft MTE012 protocol entitled, "A phase I study to evaluate the potential for interpersonal transfer of testosterone following single dose application of 2%. Testosterone Metered Dose (MD)-Lotion®." Acrux would very much appreciate FDA's comments by Friday, July 16, 2010 if at all possible.

Thank you very much.

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

Roule, Jeannie

From: Roule, Jeannie
Sent: Tuesday, July 13, 2010 4:02 PM
To: 'wilson.michelle@kendle.com'
Subject: RE: Acrux IND 70,516: MTE012 protocol_V1.0_12July10.doc

Michelle,

There are two comments for your protocol. Please update your protocol and send it in formally.

Comments for Acrux regarding their MTE12 protocol:

1. Please increase the cohort size to 10 couples.
2. Please add a female blood draw for pK at 10 hours, both on the baseline day and post-contact.

From: wilson.michelle@kendle.com [mailto:wilson.michelle@kendle.com]
Sent: Monday, July 12, 2010 3:41 PM
To: Roule, Jeannie
Subject: Acrux IND 70,516: MTE012 protocol_V1.0_12July10.doc

Dear Jeannie,

As we discussed, I've attached the Word version of the draft MTE012 protocol entitled, "A phase I study to evaluate the potential for interpersonal transfer of testosterone following single dose application of 2% Testosterone Metered Dose (MD)-Lotion®." Acrux would very much appreciate FDA's comments by Friday, July 16, 2010 if at all possible.

Thank you very much.

Best wishes,

Michelle

Michelle Wilson, Ph.D. | Principal Consultant | Global Regulatory Consulting & Submissions
Kendle International, Inc. | 441 Vine Street | Suite 500 | Cincinnati, Ohio 45202 | Ph (513) 829-1108;
Mobile (513) 578-5671 (NEW) | Fax (513) 763-7628

7/21/2010

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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

/s/

JEANNIE M ROULE

07/21/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **OSE-DRISK
REMS and Medguide review**

FROM (Name, Office/Division, and Phone Number of Requestor):
**Jeannie Roule, Project Manager, Division of
Reproductive and Urologic Products (DRUP)
301-796-3993**

DATE 5/18/10	IND NO.	NDA NO. 022504	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 05/12/10-REMS 1/25/10-NDA
------------------------	---------	--------------------------	--------------------------------	--

NAME OF DRUG Axiron (testosterone solution) 2%	PRIORITY CONSIDERATION Standard: PDUFA Date: 11/25/10	CLASSIFICATION OF DRUG Androgen	DESIRED COMPLETION DATE 10/25/10
--	---	---	--

NAME OF FIRM: **Acrux Pharma Pty Ltd**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

II. BIOMETRICS

- | | |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILTY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG SAFETY

- | | |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review Medguide and REMS. They are available in edr. Currently we do not have any label meetings scheduled.

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

JEANNIE M ROULE

05/18/2010



NDA 022504

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Acrux Pharma Pty Ltd
c/o Kendle International
441 Vine Street, Suite 500
Cincinnati, Ohio 45202

ATTENTION: Dr. Michelle Wilson
Senior Regulatory Consultant
U.S. Agent for Acrux Pharma Pty, Ltd.

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) dated January 25, 2010, received January 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Testosterone Solution 2%.

We also refer to your February 3, 2010 correspondence, received February 4, 2010, requesting review of your proposed proprietary name, Axiron. We have completed our review of the proposed proprietary name, Axiron and have concluded that it is acceptable.

The proposed proprietary name, Axiron, 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 February 3, 2010 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, Jeannie Roule, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

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

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

CAROL A HOLQUIST

05/05/2010



NDA 022504

FILING COMMUNICATION

Kendle International
Attention: Michelle Wilson
U.S. Agent for Acrux Pharma Pty Ltd.
441 Vine Street, Suite 500
Cincinnati, OH 45202

Dear Ms. Wilson:

Please refer to your new drug application (NDA) dated and received March 25, 2010, submitted under section 505 (b) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Axiron™ (testosterone solution) 2%.

We also refer to your submissions dated March 3 and April 2, 2010.

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 November 25, 2010.

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 11, 2010.

During our filing review of your application, we identified the following potential Clinical, Clinical Pharmacology and Chemistry, Manufacturing, and Controls review issues:

Clinical:

1. Individual patients with serum testosterone level >2500 ng/dl will be a review issue.
2. We will conduct a detailed review of individual patients who have an elevated hematocrit and/or hemoglobin.

Clinical Pharmacology:

3. The following will be review issues:
 - Effect of body mass index (BMI) on systemic testosterone exposure.
 - The dose titration time point and scheme.

Clinical and Clinical Pharmacology:

4. The results of transfer studies and the results of your washing study that you submitted on April 2, 2010, will be a review issue. The potential for secondary exposure of testosterone to women and children will be further considered. Additional information in labeling may be needed, including information directed to patients.

Chemistry Manufacturing and Controls:

5. For drug substance specifications, Impurities and Related Substances should not be solely listed using the European Pharmacopeia abbreviations, but should also be listed on the specification sheet with the names, e.g., Impurity (b) (4)
6. We acknowledge your statement that the oily drops in the dosage form are dimethicone and your justification on why this is not a safety concern. However, while the justification concerning the oily droplets may hold true when reviewed as it pertains to safety, there is also a question on dosing reproducibility and its effect on efficacy. Provide the following information for our review:
 - The report of the investigation concluding that the oil is dimethicone and that the source is the pump components.
 - Information on whether the oil droplets were observed in the clinical trial batches. Since stability testing was performed at different sites with different personnel, the Phase 3 clinical supply samples remaining on stability should also be evaluated to determine if the oil were present and if it were missed during stability testing.
 - Data on the amount of oil dispensed per actuation and address the effect on dose delivery and, therefore, efficacy.
 - Information on whether the same lot of (b) (4) pumps was used for the clinical trial batches and the three registration batches, and if this phenomenon were seen only with the registration batches.
 - Clarify how many actuations are performed for priming.
7. We acknowledge that the cause of the pale red coloration is currently under investigation. Submit the results of that investigation as soon as possible for our review. Address the impact on safety and efficacy of this color change. We do not agree that the Appearance acceptance criteria should be changed to include the pale red color until the reason for the color change is determined.

8. Be aware that our evaluation of the red color and oily droplets observed in your registration stability samples will have a direct impact on the expiration dating period. Supporting stability data gathered on the Phase 3 clinical supplies may not be used to set the expiration dating period if the quality of the drug product manufactured at the proposed commercial facility cannot be assured.

We also request that you submit the following information:

Clinical Pharmacology:

9. Provide us information on application surface area evaluated in the pivotal Phase 3 studies, MTB08 and MTB09.
10. Provide information on the exact application procedure instructions in Studies MTB08 and MTB09.
11. Clarify if drying time following application and treatment compliance regarding application area were assessed in Studies MTB08 and MTB09. If this were assessed, provide information regarding these aspects.
12. Clarify if potential effects of axillary hair on testosterone absorption were assessed in Studies MTB08 and MTB09. If this were not assessed in your Phase 3 studies, provide any literature or scientific information to address the potential effect of axillary hair on testosterone absorption.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must 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>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional 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.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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 Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22504	ORIG-1	ACRUX PHARMA PTY LTD	TESTOSTERONE

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/s/

GEORGE S BENSON
04/09/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP) 301-796-3993
------------------------------	--

REQUEST DATE March 25, 2010	IND NO.	NDA/BLA NO. 022504	TYPE OF DOCUMENTS: Electronic (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Axiron (testosterone solution) 2%	PRIORITY CONSIDERATION Standard: PDUFA Date:	CLASSIFICATION OF DRUG Androgen	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) September 15, 2010
--	--	------------------------------------	--

NAME OF FIRM: Acrux Pharma Pty Ltd	PDUFA Date: 11/25/10
---------------------------------------	----------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
<input type="checkbox"/> PACKAGE INSERT (PI)	<input type="checkbox"/> ORIGINAL NDA/BLA	<input type="checkbox"/> INITIAL PROPOSED LABELING
<input type="checkbox"/> PATIENT PACKAGE INSERT (PPI)	<input type="checkbox"/> IND	<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> CARTON/CONTAINER LABELING	<input type="checkbox"/> EFFICACY SUPPLEMENT	
<input type="checkbox"/> MEDICATION GUIDE	<input type="checkbox"/> SAFETY SUPPLEMENT	
<input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<input type="checkbox"/> LABELING SUPPLEMENT	
	<input type="checkbox"/> PLR CONVERSION	

EDR link to submission: This is available in edr under March 3, 2010 label

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: You can view the labeling by going to <http://edr.fda.gov>, entering the NDA 022504 and either launching global submit or viewing the labeling directly in EDR. The Applicant will most likely be asked to submit a REMS and a Med Guide. I will update you with more details at a later date. If you need anything from me, please let me know. *Please review the PI,PPI and the carton.*

Use the label dated March 3, 2010

Mid-Cycle Meeting: [Insert Date] June 23, 2010

Labeling Meetings: [Insert Dates] To be scheduled

Wrap-Up Meeting: [Insert Date] To be scheduled

SIGNATURE OF REQUESTER Jeannie Roule

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

JEANNIE M ROULE

03/25/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Division of Drug Marketing, Advertising and Communications (DDMAC)**
Attention: **Janice Maniwang 301-796-3821**

FROM (Name, Office/Division, and Phone Number of Requestor):
Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP)
301-796-3993

DATE
March 25, 2010

IND NO.

NDA NO.
022504

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
01/25/10

NAME OF DRUG
Axiron
(testosterone solution) 2%

PRIORITY CONSIDERATION
Standard:
PDUFA Date:
11/25/10

CLASSIFICATION OF DRUG
Androgen

DESIRED COMPLETION DATE
September 15, 2010

NAME OF FIRM: **Acrux Pharma Pty Ltd**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: You can view the labeling by going to <http://edr.fda.gov>, entering the NDA 022504 and either launching global submit or viewing the labeling directly in EDR. The Applicant will most likely be asked to submit a REMS and aMed Guide. I will update you with more details at a later date. If you need anything from me, please let me know.

Please review the PL,PPI and the carton.

Use the label dated March 3, 2010

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

JEANNIE M ROULE

03/25/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Controlled Substance Staff**
Corinne Moody

FROM (Name, Office/Division, and Phone Number of Requestor):
Jeannie Roule, Regulatory Project Manager
Division of Reproductive and Urologic Products
(301) 796-3993

DATE
03/25/10

IND NO.

NDA NO.
022504

TYPE OF DOCUMENT
Electronic

DATE OF DOCUMENT
01/25/10

NAME OF DRUG
Axiron
(testosterone solution) 2%

PRIORITY CONSIDERATION
Standard
PDUFA is 11/25/10

CLASSIFICATION OF DRUG
androgen

DESIRED COMPLETION DATE
06/15/2010

NAME OF FIRM: **Acrux Pharma Pty Ltd**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
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| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The PI is available in edr (dated March 3). This is a testosterone product which is considered a Class III controlled substance. If you need anything else let me know.
Your input and comments are greatly appreciated

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

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Product Name

NDA-22504

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ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

JEANNIE M ROULE

03/25/2010

REQUEST FOR CONSULTATION

TO (Office/Division): OSE-DMEPA

FROM (Name, Office/Division, and Phone Number of Requestor):
Jeannie Roule, Project Manager, Division of
Reproductive and Urologic Products (DRUP)
301-796-3993

DATE March 25,2010	IND NO.	NDA NO. 022504	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 01/25/10
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NAME OF DRUG Axiron (testosterone solution) 2%	PRIORITY CONSIDERATION Standard: PDUFA Date: 11/25/10	CLASSIFICATION OF DRUG Androgen	DESIRED COMPLETION DATE September 15, 2010
--	--	------------------------------------	---

NAME OF FIRM: Acrux Pharma Pty Ltd

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
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| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the trade name, carton and PI. It is available in edr.

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22504

ORIG-1

ACRUX PHARMA
PTY LTD

TESTOSTERONE

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/s/

JEANNIE M ROULE

03/25/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt NEW DRUG MICROBIOLOGY STAFF OC/OO/CDER/OPS/NDMS - HFD-805		FROM (Name, Office/Division, and Phone Number of Requestor): Jeannie David, Office of New Drug Quality Assessment, 301-796-4247, on behalf of Hitesh Schroff (ONDQA) 301-796-2116 and Donna Christner (ONDQA) 301-796-1341		
DATE February 09, 2009	IND NO.	NDA NO. 22-504	TYPE OF DOCUMENT Pending NDA	DATE OF DOCUMENT January 25, 2010
NAME OF DRUG testosterone solution 2%	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Friday, June 18, 2010	
NAME OF FIRM: ACRUX Pharma Pty Ltd				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> PAPER NDA <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> CONTROL SUPPLEMENT				
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): <input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> BIOAVAILABILTY STUDIES <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> PHASE 4 STUDIES <input type="checkbox"/> IN-VIVO WAIVER REQUEST				
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> POISON RISK ANALYSIS <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL <input type="checkbox"/> NONCLINICAL				
COMMENTS / SPECIAL INSTRUCTIONS: We request Product Quality Micro review for this pending NDA. This is a partial electronic submission: \\CDSESUB1\EVSPROD\NDA022504\022504.enx. The Micro reviewer during the IND stage (IND 70,516) was Bob Mello.				
SIGNATURE OF REQUESTOR {see electronic signature}		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22504	ORIG-1	ACRUX PHARMA PTY. LTD.	TESTOSTERONE

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/s/

JEANNIE C DAVID
02/09/2010



NDA 022504

NDA ACKNOWLEDGMENT

Kendle International
Attention: Lisa Jenkins, Ph.D.
U.S. Agent for Acrux Pharma Pty, Ltd.
Associate Director
441 Vine Street, Suite 500
Cincinnati, OH 45202

Dear Dr. Jenkins:

We have received your new drug application (NDA) submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: testosterone solution 2%.

Date of Application: January 25, 2010

Date of Receipt: January 25, 2010

Our Reference Number: NDA 022504

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 26, 2010, in accordance with 21 CFR 314.101(a).

The NDA number provided above should be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call Jeannie Roule, Regulatory Health Project Manager, at (301) 796-3993.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22504	ORIG-1	ACRUX PHARMA PTY. LTD.	TESTOSTERONE

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/s/

JENNIFER L MERCIER
02/02/2010