

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022504Orig1s000**

**OTHER REVIEW(S)**

## SEALD LABELING: FINAL PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22-504
APPLICANT	Lilly/ Acrux Pharma Pty Ltd
DRUG NAME	AXIRON (testosterone) topical solution
SUBMISSION DATE	25 January 2010
PDUFA DATE	23 November 2010
SEALD REVIEW DATE	19 November 2010
OND ASSOCIATE DIRECTOR FOR LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies found in the SEALD Labeling Review filed 17 November 2010 for this application have been addressed. SEALD agrees with the Division that the PI is ready for approval at this time.

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/s/  
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LAURIE B BURKE  
11/19/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date:	November 19, 2010
Application Type/Number:	NDA 022504
To:	Scott Monroe, MD, Director Division of Reproductive and Urology Products
Through:	Denise Toyer, Pharm.D., Deputy Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, Pharm.D., BCPS, Acting Team Leader Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Label and Labeling Review
Drug Name(s):	Axiron (Testosterone) Topical Solution, 30 mg of testosterone per pump actuation
Applicant:	Kendle International, Inc.
OSE RCM #:	2010-367

## **1 INTRODUCTION**

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the revised labels and labeling for Axiron submitted by the Applicant on November 18, 2010 by e-mail to the Division of Reproductive and Urologic Products (DRUP). DMEPA previously reviewed Axiron labels and labeling in OSE Review #2010-367 dated June 3, 2010 and OSE Review #2010-367 dated October 7, 2010.

## **2 MATERIALS REVIEWED**

DMEPA reviewed the revised labels and labeling received on November 18, 2010 (see Appendices A and B). We compared the revised labels and labeling against the recommendations contained in OSE review # 2010-367 dated October 7, 2010.

## **3 RESULTS AND CONCLUSIONS**

Review of the revised documents show that the Applicant implemented DMEPA's recommendations under OSE review #2010-367. The revised labels and labeling are also reflective of recommendations agreed upon between the Office of New Drug Quality Assessment (ONDQA) and DMEPA. DMEPA has no additional recommendations at this time.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

## **4 REFERENCES**

*OSE Review #2010-367, Label and Labeling Review for Axiron. Chan, I: June 3, 2010.*

*OSE Review #2010-367, Label and Labeling Review for Axiron. Chan, I: October 7, 2010.*

**Appendix A: Revised Retail Container Label (front panel and back panel)**



**Appendix B: Revised Retail Carton Labeling**

(b) (4)



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/s/  
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IRENE Z CHAN  
11/19/2010

DENISE P TOYER  
11/19/2010

## SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22504
APPLICANT	Eli Lilly
DRUG NAME	AXIRON (testosterone)
SUBMISSION DATE	January 25, 2010
PDUFA DATE	November 23, 2010 (tentative November 19, 2010)
SEALD REVIEW DATE	November 17, 2010
SEALD LABELING REVIEWER	Elisabeth Piauult-Louis; Jun Yan

Outlined below are the following outstanding labeling issues that must be corrected before the final draft labeling is approved. Issues are listed in the order mandated by the regulations or guidance.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), “none” is stated. If clearly inapplicable sections are omitted from the FPI, “not applicable” is stated. In addition, “not applicable” is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

### Highlights (HL):

- The HL section is longer than ½ page; however, the sponsor obtained a waiver. Add a column break before “Contraindications” to obtain even lengths between the columns.
  - **Highlights Limitation Statement:** None
  - **Product Title Line:** None
  - **Initial U.S. Approval:** None
  - **Boxed Warning:** None
  - **Recent Major Changes:** NA
  - **Indications and Usage:** None
  - **Dosage and Administration:** None
  - **Dosage Forms and Strengths:** None

## SEALD LABELING REVIEW

- **Contraindications:** None
- **Warnings and Precautions:** None
- **Adverse Reactions:**
  - o Is the contact name (Acrux Pharma Pty Ltd) accurate since Eli Lilly is marketing Axiron in US?
- **Drug Interactions:** None
- **Use in Specific Populations:** None
- **Patient Counseling Information Statement:** None
- **Revision Date:** None

*Table of Contents (TOC):* None

*Full Prescribing Information:*

### **Boxed Warning:**

- 1 Indications and Usage:** None
- 2 Dosage and Administration:** None
- 3 Dosage Forms and Strengths:** None
- 4 Contraindications:**
  - o Add a bullet before “AXIRON is contraindicated in women.”
- 5 Warnings and Precautions:** None
- 6 Adverse Reactions:** None
- 7 Drug Interactions:** None
- 8 Use in Specific Populations:** None
- 9 Drug Abuse and Dependence:** None

## SEALD LABELING REVIEW

**10 Overdosage:** None

**11 Description:** None

**12 Clinical Pharmacology:** None

**13 Nonclinical Toxicology:** None

**14 Clinical Studies:** None

**15 References:** Not applicable

**16 How Supplied/Storage and Handling:** None

**17 Patient Counseling Information:** None

The revision date at the end of highlights replaces the “revision” or “issued” date at the end of the prescribing information. (b) (4)

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/s/  
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JUN YAN  
11/17/2010

ANN M TRENTACOSTI  
11/17/2010

MEMORANDUM

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

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DATE: October 28, 2010

TO: Scott E. Monroe, M.D.  
Director, Division of Reproductive and Urologic  
Products (DRUP), Office of Drug Evaluation III

Edward D. Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology III,  
Office of Clinical Pharmacology

FROM: Sripal R. Mada, Ph.D. and Sean Y. Kassim, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 10/28/10*  
Acting Team Leader, Bioequivalence  
GLP and Bioequivalence Branch  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-504, Axiron™  
(Testosterone solution, 2%), from Acrux Pharma Private  
Limited

At the request of the Division of Clinical Pharmacology-3 (DCP3), the Division of Scientific Investigations (DSI) conducted an inspection of the clinical and analytical portions of the following studies:

- MTE06**: "A Phase I, three part study to evaluate the potential for interpersonal transfer and to determine the impact of application of antiperspirant and deodorant, and the impact of washing the application site, on the pharmacokinetics of testosterone following single dose application of Testosterone Metered dose (MD)-Lotion®"
- MTE07**: "A Phase II, randomized, four-way crossover study to compare the steady state pharmacokinetics of testosterone following application of different Testosterone Metered dose (MD) lotion® formulations and doses in hypogonadal men"
- MTE08**: "A Phase III open-label titration trial to evaluate the effectiveness and safety of different doses (30 mg, 60 mg, 90 mg, and 120 mg) of a dermal application of Testosterone

MD-Lotion® (cutaneous solution, 2%) via the axilla in hypogonadal men"

**MTE09**: "A Phase III open-label extension of the MTE08 trial (A Phase III open-label titration trial to evaluate the effectiveness and safety of different doses (30 mg, 60 mg, 90 mg, and 120 mg) of a dermal application of Testosterone MD-Lotion® (cutaneous solution, 2%) via the axilla in hypogonadal men) to evaluate skin-safety"

**MTE10**: "A Phase I, randomized, open-label, single center, parallel group, single dose study to determine the impact of application of antiperspirant and deodorant as well as washing the application site, on the pharmacokinetics of testosterone following single dose applications of Testosterone MD-Lotion® 2% (cutaneous solution) in healthy female subjects"

**CLINICAL INSPECTIONS:**

Inspections of clinical portions were conducted for study MTE08 and MTE09 at:

**Site-1: Regional Urology (Regional), Shreveport, LA**

**Site-2: Deerfoot Internal Medicine (Deerfoot), Birmingham, AL**

**Site-3: Northwest Clinical Trials (Northwest), Boise, ID**

**Regional Audit**: Following inspection at the clinical site-1 (Regional Urology, Shreveport, LA) during July 22-23, 2010, no Form FDA-483 was issued.

**Deerfoot Audit**: Following inspection at the clinical site-2 (Deerfoot Internal Medicine, Birmingham, AL) during August 3-4, 2010, no Form FDA-483 was issued.

**Northwest Audit**: Following inspection of clinical site-3 (Northwest Clinical Trials, Boise, ID) during August 2-5, 2010, Form FDA-483 was issued (**Attachment MPK1**). The firm's response was received on August 16, 2010 (see **Attachment MPK2**).

The Form FDA-483 observations for studies MTE08 and MTE09, response to Form FDA-483 and our evaluations follow:

**1. Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study related tests.**

The clinical site performed pre-screening evaluations on subjects without obtaining study specific informed consent. However, a General Health Screen Information and Consent Form, that was not IRB approved, was signed by the subjects prior to evaluating them for pre-screening for the study. The clinical investigator (CI) stated during the inspection that he was considering the subjects identified in the 483 observation for inclusion in the study, but did not think that a study specific informed consent was necessary for pre-screening.

The CI indicates he discontinued the practice of pre-screening until he obtains guidance from an institutional review board (IRB) as well as an IRB approved consent form for general screening. Additionally, the response indicated the information collected during the pre-screen evaluations was not used as data for the clinical investigation. DSI considers this response acceptable.

**2. A consent form, not approved by the IRB, was used to screen subjects for a clinical study. This unapproved consent form did not include a statement that they were being screened for a research study.**

The CI used a pre-screening general health form that was not IRB approved. In his response, the CI indicated that two IRBs advised him that such a pre-screening health form did not require IRB approval. He admits he should have sought guidance directly from FDA. He agrees to obtain IRB approval for pre-screening general health consent form.

**ANALYTICAL INSPECTIONS:**

Inspections of analytical portions were conducted for total testosterone (TT), dihydrotestosterone (DHT) and sex hormone binding globulin (SHBG) at:

**Site-1:** [REDACTED] (b) (4)  
(study MTE06 for TT, DHT, and SHBG)

**Site-2:** [REDACTED] (b) (4)  
(studies MTE07, MTE08, MTE09 and MTE10 for TT and DHT)

Site-3: [REDACTED] (b) (4)  
[REDACTED] (b) (4) (studies MTE07, MTE08, MTE09 and MTE10 for SHBG)

(b) (4) **Audit:** Following our inspection of [REDACTED] (b) (4) Form FDA-483 was issued (**Attachment SYK1**). The firm's response (dated September 7, 2010) was received on September 8, 2010 (**Attachment SYK2**).

*Note: A mass spectrometric assay was used for TT, and a ligand-binding assay (LBA) was used for DHT and SHBG.*

The Form FDA-483 observations for study MTE06, response to Form FDA-483 and our evaluations follow:

**1. Many analytical runs had > 33.3% of the total QCs and/or > 50% of the QCs at the same concentration with deviations > 15% (for MS-based assays) or 20% (for ligand-based assays) from the nominal concentrations or mean pooled QC concentrations. These analytical runs are listed below:**

**TT: Runs 07060694, 07062970, 07062971, 07063073, 07070796, 07080981**

**DHT: Runs 07062884, 07070704, 07070806, 07080742, 07081156, 07081875**

**SHBG: Run 07060745**

Instead of following the recommendations in FDA's Bioanalytical Method Validation Guidance, [REDACTED] (b) (4) used Westgard rules (common in diagnostics) to accept or reject analytical runs. During the inspection, the firm was requested to re-calculate the QC results in each run using criteria listed in the FDA Guidance (i.e., reject a run when > 33.3% of total # of QCs and/or > 50% of QCs at the same concentration with deviations > 15% (for MS based assays) or 20% (for ligand-based assays) from the nominal concentrations). The above listed runs failed the run acceptance criteria used in the FDA Guidance. It is important to note that, in most runs, the firm also included clinical diagnostic samples not related to the study. A list of subject samples in the failed runs is provided in Attachments **SYK3**, and **SYK4**. Attachment **SYK3** shows subject samples included in the failed TT runs, and Attachment **SYK4** includes sorted subject samples included in the failed DHT runs. The study samples in the failing SHBG run were repeated in a later run after dilution.

[REDACTED] (b) (4) response indicated they currently use 15% or 20% criteria for acceptance of LC/MS or LBA assays, respectively,

but during the conduct of the study, only the Westgard rules were in place. Additionally, they indicated that discussion with the sponsor led them to re-evaluate all the raw data for TT with global integration parameters. This reprocessing resulted in 122 failed samples out of 1214 total analyzed. The results of this reprocessing were not provided in the response. However, (b)(4) is providing the sponsor an amended report identifying data from batches that failed FDA recommended acceptance criteria.

The DHT samples from runs failing the Bioanalytical guidance criteria in study MTE06 could not be re-quantified due to the nature of the LBA and the SHBG samples from run 07060745 were already repeated as dilutions in a separate batch.

We recommend that the TT and DHT samples identified be removed and the data re-analyzed. The re-processed TT data using global integration parameters should be evaluated when provided by the Sponsor.

**2. Failure to reject analytical runs when > 25% of calibration standards in a standard curve failed to meet the acceptance criteria (> 15% or > 20% (LLOQ) deviation from nominal values). Additionally, TT run TESMMS07062767 for study MTE06 was improperly accepted despite failing standards - quantitation was performed substituting the standards from a previous run (TESMMS07062665).**

(b)(4) calculated TT concentrations of samples in run TESMMS07062767 using a standard curve from a previous run. The standard curve for run TESMMS07062767 had < 75% of the calibrators within the acceptance criteria. The TT samples included in the run are listed in Attachment **SYK3**.

The firm's response indicates the TT results from MTE06 were reprocessed using global parameters. The run 07062767 failed after requantification and are expected to be identified in the amended report sent to the sponsor.

We advise the Division to expect the amended report from the sponsor. We recommend the re-processed data be evaluated.

**3. Failure to use the appropriate QC values during analysis. For example, one testosterone and four SHBG QCs for study MTE06 used incorrect concentrations for some of the run acceptance criteria.**

The TT and SHBG runs using incorrect QC concentrations were reviewed. The TT QC results using lot TESM4A remain acceptable

with the correct concentration. The SHBG QC errors did not affect acceptance of any runs.

(b) (4) response indicates that the observed errors were only in their analytical report, and that the actual run acceptance/rejection decisions used the correct values. The firm indicated that they would require additional review and approval to complete future final reports.

DSI recommends this is acceptable.

**4. Failure to accurately demonstrate appropriate analyte stabilities. Room temperature serum and whole blood stabilities of testosterone concentrations below 200 ng/dL were not evaluated.**

Room temperature stability was not established for either whole blood or serum testosterone below 200 ng/dL. (b) (4) was not informed of the processing times at room temperature at the clinical sites. However, the 8 ng/dL QC was stable during study analyses, relative to similarly-handled calibrators.

The firm's response included two new studies establishing testosterone stability at room temperature for 50, 10, and 8 ng/dL in serum for 4 days and for approximately 21, 30, and 54 ng/dL in whole blood for 2 hours. Evaluation of stability in whole blood at room temperature for 24 hours failed.

DSI recommends the sponsor should ascertain that whole blood samples were processed within established limits.

**5. Audit trail of the 'Analyst' software version 1.4.1 was not enabled for all the validation and analytical runs. There are no audit trail records available for inspection and multiple samples were manually integrated without audit trails.**

The inspection could not determine whether manual integrations affected run outcomes, and the absence of audit trails prevents reconstruction of changes made to the data.

(b) (4) response indicates the TT data have been reprocessed using global integration parameters as discussed above. These data were not provided in the response. DSI recommends using the data processed with the global parameters.

**6. Failure to document sufficient preparation details to reconstruct the determination of two SHBG runs. For MTE06, records for SHBG runs 07060540 and 07080549 did not have complete assay preparation detail.**

The records for SHBG runs 07060510 and 07080549 did not identify the standards and reagents used for these runs. The SHBG samples included in these runs are listed in Attachment **SYK5**.

(b)(4) response indicates that the missing details were limited to a few reagents, all of which were released for use within their expiration dates. They indicate that they will require further review and approval in the future.

DSI recommends the identified samples be omitted and the data re-analyzed.

Please note all SYK attachments are available as MS-Excel® files to allow sorting if required.

(b)(4) **Audit:** Following our inspection of (b)(4) Form FDA-483 was issued (**Attachment SRM1**). The firm's response (dated August 19, 2010) was received on September 28, 2010 (by an email attachment, see **Attachment SRM2**).

*Note: A mass spectrometric assay was used for TT and DHT.*

The Form FDA-483 observations for studies MTE07, MTE08, MTE09 and MTE10, response to Form FDA-483 and our evaluations follow:

**1. Failure to use calibration standards and quality control (QC) samples that were representative of the testosterone and dihydrotestosterone (DHT) concentrations in subject serum samples. Specifically, the mean  $C_{max}$  values for studies MTE07 and MTE10 range 220.6 ng/dL to 589.0 ng/dL (testosterone), 54.4 ng/dL to 92.2 ng/dL (DHT), but the QC samples were 80.2, 1020, 1820 and 4020 ng/dL (testosterone in female serum), 24.9, 260, 460 and 1010 ng/dL (DHT in female serum) for low, mid1, mid2 and high, and calibrator samples were 20, 40, 100, 500, 1500, 2000, 2500, 4520 and 5000 ng/dL (testosterone in PBS), 5, 10, 25, 125, 374, 499, 624, 1120 and 1250 ng/dL (DHT in PBS).**

The mid2 and high QC samples and 4 of 9 testosterone and 5 of 9 DHT calibrators were not representative of the testosterone and DHT concentrations obtained in study subjects. The observed TT and DHT concentrations were significantly lower than most of the calibrators and QCs.

In their response to Form FDA-483, (b)(4) stated that they selected calibrators based on published literature (expected  $C_{max}$  5-250 ng/mL), and that expected  $C_{max}$  values were not included in the package insert for the marketed reference drug product (Vivactil® Tablets).

Following a review of all QC results, DSI notes that almost all the mid1 QC samples and low QC samples passed in all analytical runs. DSI is of the opinion that this observation should have no significant impact on accuracy of the reported TT and DHT serum concentrations.

**2. Failure to provide accuracy study for the use of PBS as matrix for calibrators in studies MTE07, MTE08, MTE09 and MTE10.**

Specifically, calibrators were prepared in phosphate-buffered saline (PBS). However, measurement accuracy using QCs prepared in charcoal stripped serum was not provided.

(b)(4) response to Form FDA-483 observations included data from QCs prepared with known TT and DHT concentrations added to a pool of female human serum. The results showed good recovery of added TT and DHT.

DSI recommends that the supplementary data are sufficient to justify the used of PBS-based calibrators.

**3. Failure to use freshly prepared QC samples in the frozen matrix stability studies for testosterone and DHT.**

The reported frozen stability study is questionable, as results of the stability QC samples were not compared to freshly prepared reference QC samples. During the inspection, DSI noted that the reference QCs were prepared and frozen a day prior to analysis and they considered these samples as fresh.

In their response to Form FDA-483, (b)(4) acknowledged this observation and revised their SOP and now requires using fresh reference QCs.

DSI recommends that (b)(4) should demonstrate stability of TT and DHT by comparing results of the stability QC samples to results of the freshly-prepared reference QC samples or their nominal values in future studies. The matrix stability studies for TT and DHT audited in the present inspection are found to be acceptable when results of the stability QC samples were compared to the nominal values.

**4. Failure to evaluate Incurred Sample Re-analysis (ISR) in studies MTE07, MTE08, MTE09 and MTE10.**

In their response to From FDA-483, (b)(4) acknowledged this observation and stated that they revised their SOP for ISR only after the Crystal City Meeting on April 15, 2009. However, DSI noted that Studies MTE07, MTE08, MTE09 and MTE10 were conducted

after the February 8, 2008 Crystal City, Arlington, VA meeting (Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples-Implications of Crystal City Recommendations).

DSI recommends that ISR is an important aspect of accuracy and precision in assays for TT and DHT. Without valid ISR data, the accuracy and precision of study data are not assured.

**5. Failure to investigate transport conditions and stability of 73 total samples for studies MTE07, MTE08 and MTE09 received from the (b) (4) when the manifest from (b) (4) indicated the samples were received from the Clinical Investigator sites in an ambient temperature state.**

In their response to Form FDA-483, (b) (4) stated that they investigated the samples in question for studies MTE07, MTE08 and MTE09. The samples from one subject used in the PK data were within the demonstrated stability for study MTE07. The majority of the samples from MTE08 and MTE09 were spares, not used in the PK analyses.

DSI recommends that this observation has no impact on data integrity for the studies.

**(b) (4) Audit:** Following our inspection of (b) (4) (August 2-17, 2010) Form FDA-483 was issued (**Attachment SRM3**). The (b) (4) response (dated September 03, 2010) was received on September 9, 2010 (by an email attachment, see **Attachment SRM4**).

*Note: An Enzyme Immuno Assay (EIA) was used to measure SHBG.*

The Form FDA-483 observations for studies MTE07, MTE08, MTE09 and MTE10, response to Form FDA-483 and our evaluations follow:

**1. Failure to use appropriate quality control (QC) samples in analytical runs. Specifically, only a total of 3 QCs were used in each run; two QCs were from pooled patient serum samples and one QC (in buffer) was from the supplies with the kit. Moreover, the nominal value of the serum QCs was not confirmed and the buffer QC was in a different matrix from subject serum samples. The SHBG concentrations in the serum QCs were not uniform and were different from run to run.**

The firm used Westgard rules to accept or reject analytical runs. They did not use the run acceptance criteria listed in the 'FDA Guidance for Industry - Bioanalytical Method Validation'. Moreover, (b) (4) used only two QCs from pooled patients' serum samples and one buffer-based QC in duplicates. The matrix used

to prepare the QC samples were not representative of the study subject samples, as pooled patients' serum and the buffer were used in place of QC prepared by spiking SHBG solution in blank serum. DSI also has a concern that the true SHBG concentrations in the QC samples prepared from pooled patient samples can not be confirmed.

DSI recommends that the QC samples used in studies MTE07, MTE08, MTE09 and MTE10 do not assure the accuracy of reported SHBG concentrations.

## **2. Failure to evaluate Incurred Sample Reproducibility (ISR) for the SHBG assay.**

(b) (4) responded that they evaluated one year stability using pooled serum QCs during method validation. DSI recommends that ISR should be evaluated in individual donors' samples, not in pools, and under the exact conditions as used during the study. DSI recommends that important parts of accuracy and precision in the SHBG data cannot be confirmed.

**3. During the inspection, (b) (4) could not provide a report for the analysis of SHBG in study samples, and the supporting raw SHBG data were not maintained in a readily accessible form. Although (b) (4) attempted to provide the raw SHBG data records in a reviewable form as requested, the records were available only at the very end of the inspection.**

(b) (4) did not generate a bioanalytical report for the assays of SHBG in these studies. (b) (4) could not retrieve raw data for the assays in a reviewable form until near the end of an extended inspection.

Subsequently (b) (4) provided copies of all raw data to DSI for further review. DSI found no additional inconsistencies in the supplementary raw data.

## **Conclusions:**

Following the inspections, DSI recommends that:

### **(b) (4) Audit:**

- The TT and DHT results for samples listed in Attachments **SYK3**, and **SYK4** should be excluded from review and the study outcomes should be re-evaluated using the remaining data. The reprocessed TT data using global integration parameters should be evaluated when produced by the sponsor (see (b) (4) **Items 1, 2** for details).

- (b) (4) provided room temperature stability for TT in serum at concentrations less than 200 ng/dL. Stability for TT in whole blood at room temperature at concentrations less than 200 ng/dL was established for only two hours. The sponsor should ascertain whether the study conditions were within these limits. (see (b) (4) **Item 4**).
- The lack of audit trail precludes a complete evaluation of events during the TT analyses. Nevertheless, DSI recommends that the (b) (4) TT runs can be accepted (see (b) (4) **Item 5**). However, the sponsor should provide the updated data from the reintegration reprocessing, containing the full audit trail.
- The SHBG data from incompletely documented SHBG runs (**SYK5**) should be excluded from evaluation. The SHBG portion of the study should be re-evaluated using the remaining data (see (b) (4) **Item 6**).

(b) (4) **Audit:**

- (b) (4) did not conduct the ISR study. Without valid ISR data, the accuracy and precision of study data are not assured.

(b) (4) **Audit:**

- The QC samples were not representative of the study subject samples, as pooled patients' serum and the buffer were used in place of QC prepared by spiking SHBG solution in blank serum. Thus, the results of QC samples used in these studies (MTE07, MTE08, MTE09 and MTE10) do not assure valid acceptance / rejection for each run. DSI recommends that the SHBG data for studies MTE07, MTE08, MTE09 and MTE10 are not acceptable for review (see (b) (4) **Item 1**).
- (b) (4) did not conduct the ISR study. Without valid ISR data, the accuracy and precision of study data are not assured.

**Northwest Audit:**

- The clinical investigator did not obtain IRB approval of the pre-screening consent form used in these studies. However, the proposed corrective action is

sufficient to prevent recurrence in the future. (NCT Items 1-2).

After you have reviewed this transmittal memo, please append it to the original NDA submission.



Sripal R. Mada, Ph.D.



Sean Y. Kassim, Ph.D.

**Final Classification:**

**NAI - Regional Urology, Shreveport, LA**

FEI: 3008415613

**NAI - Deerfoot Internal Medicine, Birmingham, AL**

FEI: 3008415634

**VAI - Northwest Clinical Trials, Boise, ID**

FEI: 3008471015

(b) (4)

cc:

DSI/Ball

DSI/GLPBB/Mada/Kassim/Rivera-Lopez/Yau/Haidar/CF

OCP/DCP3/Bashaw/Kim/Yu

ODE3/DRUP/Monroe/Roule

HFR-CE750/Olenjack

HFR-PA2535/Hall

HFR-PA3540/Kelly-Doggett/Brown

Draft: SRM 10/18/10, 10/22/10; SYK 08/24/10, 10/25/10

Edit: MKY 10/19/10, 10/28/2010; MFS 10/19/10

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/s/  
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SRIPAL R MADA

10/29/2010

Original signed documents are available in DSI file.

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**PATIENT LABELING REVIEW**

Date: **October 25, 2010**

To: **Scott Monroe, MD., Director  
Division of Reproductive and Urologic Products  
(DRUP)**

Through: **LaShawn Griffiths, RN, MSHS-PH, BSN  
Acting Team Leader, Patient Labeling Reviewer  
Division of Risk Management (DRISK)**

**Melissa Hulett, MSBA, BSN, RN  
Patient Labeling Reviewer  
Division of Risk Management (DRISK)**

From: **Shawna Hutchins, MPH, BSN, RN  
Patient Labeling Reviewer  
Division of Risk Management (DRISK)**

Subject: **DRISK Review of Patient Labeling (Medication  
Guide)**

Drug Name  
(established  
name): **AXIRON (testosterone)**

Dosage Form  
and Route: **Solution for Topical Use**

Application  
Type/Number: **NDA 22-504**

Applicant: **Acrux Pharma Pty Ltd.**

OSE RCM #: **2010-1107**

## 1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), for AXIRON (testosterone) Solution for topical use.

On January 25, 2010 the applicant's submitted NDA 22-504 for AXIRON (testosterone) Solution for topical use for the treatment of males with a deficiency or absence of endogenous testosterone.

The Review of the Risk Evaluation and Mitigation Strategy (REMS) will be provided under separate cover.

## 2 MATERIAL REVIEWED

- Draft AXIRON (testosterone) Medication Guide (MG) received on May 12, 2010 and sent to DRISK on October 07, 2010.
- Draft AXIRON (testosterone) prescribing information (PI) received March 03, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on October 07, 2010.
- Approved comparator labeling for Androgel 1% (testosterone), dated September 18, 2009.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG, the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

## 4 CONCLUSIONS

The MG is acceptable with our recommended changes.

## **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

**Appendix A: Medication Guide (Marked Copy)**

15 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)  
immediately following this page.

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/s/

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SHAWNA L HUTCHINS  
10/25/2010

LASHAWN M GRIFFITHS  
10/26/2010

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**\*\*\*PRE-DECISIONAL AGENCY MEMO\*\*\***

---

Date: October 14, 2010

To: Jeannie Roule, Regulatory Project Manager  
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer  
Beth Carr, Pharm.D., Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022504**  
DDMAC labeling comments for Axiron™ (testosterone solution) 2%

---

**Background**

This consult is in response to DRUP's March 25, 2010 request for DDMAC's review on labeling materials for Axiron™ (testosterone solution) 2% (Axiron). DDMAC has reviewed the following labeling materials for Axiron:

Healthcare Provider Directed:

- Prescribing Information (PI)

Consumer Directed:

- Medication Guide (Med Guide)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on October 7, 2010. In addition, we have considered the AndroGel 1% PI (approved September 2009) and Testim 1% PI (approved September 2009) in our review of the draft Axiron labeling.

We offer the following comments:

**PI & PPI**

Please see our attached comments.

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)  
(301) 796-3821, or [janice.maniwang@fda.hhs.gov](mailto:janice.maniwang@fda.hhs.gov)
- Beth Carr (Consumer directed materials)  
(301) 796-3674, or [beth.carr@fda.hhs.gov](mailto:beth.carr@fda.hhs.gov)

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/s/

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JANICE L MANIWANG  
10/15/2010

BETH M CARR  
10/15/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: October 7, 2010

Application Type/Number: NDA 022504

To: Scott Monroe, MD, Director  
Division of Reproductive and Urology Products

Through: Melina Griffis, RPh, Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Axiron (Testosterone) Solution, 2%

Applicant: Kendle International, Inc.

OSE RCM #: 2010-367

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## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the revised labels and labeling for Axiron submitted by the Applicant on August 16, 2010. DMEPA previously reviewed Axiron labels and labeling in OSE Review #2010-367 dated June 3, 2010.

## 2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised labels and labeling submitted on August 16, 2010 (see Appendices A and B). In addition, we compared the revised labels to those reviewed in OSE Review #2010-367 dated June 3, 2010 (see Appendices C and D) to evaluate whether the Applicant addressed our previous label and labeling recommendations.

## 3 CONCLUSIONS AND RECOMMENDATIONS

In an attempt to address our previous label and labeling recommendations, the Applicant has introduced new areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 Comments to the Division. We request the recommendations for the carton labeling and container label in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

### 3.1 COMMENTS TO THE DIVISION

#### A. HIGHLIGHTS OF PRESCRIBING INFORMATION

##### 1. Dosage Forms and Strengths Subsection

As currently presented, the statement (b) (4) may be confusing. We recommend changing the statement to read *One metered-dose pump capable of dispensing 60 metered pump actuations. One full pump actuation delivers 30 mg of Axiron.*

#### B. FULL PRESCRIBING INFORMATION

##### 1. Section 3 - Dosage Forms and Strengths Subsection

See comment A(1) above.

##### 2. Section 16 – How Supplied/Storage and Handling

Under 16.1, we recommend revising for clarity to the following: *Axiron (testosterone) solution 2% is available as a metered-dose pump containing 110 mL of solution. The metered-dose pump is capable of dispensing 60 metered pump actuations. One full pump actuation delivers 30 mg of Axiron.*

## 3.2 COMMENTS TO THE APPLICANT

### 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 reads [REDACTED] (b) (4) to avoid redundancy.
4. Remove the statement [REDACTED] (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 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.

**Appendix A: Revised Retail Container Label (front panel and back panel)**



(b) (4)

**Appendix B: Revised Retail Carton Labeling**

(b) (4)



**Appendix C: Originally Proposed Retail Container Label (front panel and back panel)**

(b) (4)



**Appendix D: Originally Proposed Retail Carton Labeling**

(b) (4)



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/s/

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IRENE Z CHAN  
10/07/2010

MELINA N GRIFFIS  
10/07/2010

DENISE P TOYER  
10/08/2010



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

**Date:** June 10, 2010

**To:** Scott Monroe, M.D., Director  
Division of Reproductive and Urologic Products

**Through:** Michael Klein, Ph.D., Director  
Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff (CSS)

**From:** James M. Tolliver, Ph.D., Pharmacologist, CSS

**Subject:** Consult on NDA 22-504 - AXIRON (testosterone solution) 2 % -  
Indicated for testosterone replacement therapy in hypogonadal  
males.  
Sponsor: Acrux Pharma Pty Ltd.

**Materials reviewed:** All materials submitted and comprising NDA 22-504.

**Background:**

The Division of Reproductive and Urologic Products submitted a consult to CSS for comment on NDA 22-504 for AXIRON under development by Acrux Pharma Pty Ltd. CSS verified the scheduling status of AXIRON and assessed the labeling for AXIRON as it applies to abuse and dependence.

AXIRON is formulated as a single-phase solution containing 2% w/v testosterone, octisalate (b) (4) povidone (b) (4) and (b) (4) isopropyl alcohol (IPA) (b) (4) and (b) (4) ethanol. The product will be applied via a metered-dose pump utilizing a standard manual pump and nozzle which is designed to deliver a unit volume (1.5 mL containing 30 mg testosterone) of the formulation uniformly to an applicator which is then used to apply the product to the skin under the armpit (axilla). Indicated doses include, 30 mg, 60 mg, 90 mg or 120 mg once daily. It is intended for testosterone replacement therapy in males with a deficiency or absence in endogenous testosterone due either to primary hypogonadism (congenital or acquired) or to hypogonadotropic hypogonadism (congenital or acquired).

**Conclusions and Recommendations**

AXIRON is controlled in Schedule III of the Controlled Substances Act. Testosterone is specifically designated a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii).

### Proposed Labeling of AXIRON

Currently, the draft labeling under "9. DRUG ABUSE AND DEPENDENCE" reads as follows:

#### 9.1 Controlled Substance

AXIRON contains testosterone, a Schedule III controlled substance as defined by the Anabolic Steroids Control Act.

CSS recommends that the labeling under "9. DRUG ABUSE AND DEPENDENCE" be changed to read as follows:

#### 9.1 Controlled Substance.

AXIRON contains testosterone, a Schedule III controlled substance in the Controlled Substances Act (CSA).

#### 9.2 Abuse and Addiction

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

#### 9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- 1) taking more drug than intended
- 2) continued drug use despite medical and social problems
- 3) significant time spent in obtaining adequate amounts of drug
- 4) desire for anabolic steroids when supplies of the drugs are interrupted
- 5) difficulty in discontinuing use of the drug despite desires and attempts to do so
- 6) experience of a withdrawal syndrome upon discontinuation of anabolic steroid use.

The withdrawal syndrome can last for weeks or months and includes depressed mood, fatigue, craving, restlessness, anorexia, insomnia and decreased libido.

### **Discussion**

With respect to scheduling status, the label should state that AXIRON is in Schedule III under the Controlled Substances Act of 1970, and not under the Anabolic Steroids

Control Act. This latter legislation simply amended the Controlled Substances Act to place anabolic steroids, including testosterone, into Schedule III.

Currently, the labeling suffers from a lack of information regarding abuse or dependence and should be updated. We recommend that some general class information regarding anabolic steroid abuse and dependence be added to the Abuse and Dependence section of the label. This information would at least alert the reader that abuse and dependence development is a possibility and should be considered when they store, dispense or use an anabolic steroid. Similar general information should be considered for the labeling of other products containing testosterone and other anabolic steroids.

Over the years, a considerable scientific and medical literature has accumulated documenting the abuse of anabolic steroids by athletes and bodybuilders; patterns of abuse and physical and psychiatric adverse effects are described. Several recent review articles on this topic include Brower (2002), Hartgens and Kuipers (2004), Trenton and Currier (2005), and Pope and Brower (2009). In addition, there is evidence that abuse of high doses of anabolic steroids can lead to dependence. A number of studies with athletes using high doses of anabolic steroids examine dependence according to the DSM diagnostic criteria for substance abuse dependence (Brower et al, 1991; Gridley and Hanrahan, 1994; Pope and Katz, 1994; Malone et al., 1995; Copeland et al., 1998; Midgley et. al., 1999; Perry et al, 2005; and Kanayama et al., 2009). In addition, a specific withdrawal syndrome upon termination of prolonged high dose anabolic steroids has been identified. Recently, a group of researchers published a paper in the American Journal of Psychiatry suggesting the future addition in DSM-V of specific diagnostic criteria for dependence to anabolic-androgenic steroids (Kanayama et al., 2009). Recent review articles concerning dependence on anabolic steroids include Brower (2002), Pope and Brower (2009), Quaglio et al, 2009 and Wood (2008).

## **References**

Brower KJ, Blow FC, Young JP and Hill EM (1991). Symptoms and correlates of anabolic-androgenic steroid dependence. *British Journal of Addiction*, 86: 759-768

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Copeland J, Peters R and Dillon P (1998). A study of 100 anabolic-androgenic steroid users. *Medical Journal of Australia*, 311-312.

Gridley DW and Hanrahan SJ (1994). Anabolic-androgenic steroid use among male gymnasium participants: dependence, knowledge, and motives. *Sport Health*, 12: 11-14.

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Midgley SJ, Heather N and Davies JB (1999). Dependence-producing potential of anabolic-androgenic steroids. *Addiction Research*, 7: 539-550.

Malone DA., Dimeff RJ, Lombardo JA and Sample RH (1995). Psychiatric effects and psychoactive substance use in anabolic-androgenic steroid users. *Clinical Journal of Sports Medicine*, 5: 25-31.

Perry PJ, Lund BC, Deninger MJ, Kutscher EC and Schneider J (2005). Anabolic steroid use in weightlifters and bodybuilders: an internet survey of drug utilization. *Clinical Journal of Sport Medicine*, 15: 326-330.

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Pope HG and Katz DL (1994). Psychiatric and medical effects of anabolic-androgenic steroid use: a controlled study of 160 athletes. *Archives of General Psychiatry*, 51: 375-382.

Quaglio G, Fornasiero A, Mezzelani P, Moreschini S, Lugoboni F and Lechi A (2009). Anabolic steroids: dependence and complications of chronic use. *Intern Emerg. Med.*, 4: 289-296.

Talih F, Fattal O and Malone D (2007). Anabolic steroid abuse: psychiatric and physical costs. *Cleveland Clinic Journal of Medicine*, 74: 341-352.

Trenton AJ and Currier GW (2005). Behavioral manifestations of anabolic steroid use. *CNS Drugs*, 19: 571-595.

Wood RI (2008). Anabolic-androgenic steroid dependence? Insights from animals and humans. *Frontiers in Neuroendocrinology*, 29: 490-506

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

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SILVIA N CALDERON  
06/10/2010

MICHAEL KLEIN  
06/11/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: June 3, 2010

To: Scott Monroe, MD, Director  
Division of Reproductive and Urology Products

Through: Melina Griffis, RPh, Team Leader  
Denise Toyer, Pharm.D., Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Axiron (Testosterone) Solution, 2%

Application Type/Number: NDA 022504

Applicant: Kendle International, Inc.

OSE RCM #: 2010-367

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## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the proposed labels and labeling for Axiron for areas of vulnerability that can lead to medication errors. We provide recommendations in Section 3 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

## 2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the labels and labeling submitted as part of the January 25, 2010 original submission (see Appendices A and B). Additionally we looked at previous label and labeling reviews (OSE # 2009-897 and 2009-334) for testosterone products to ensure consistency when making recommendations.

## 3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 Comments to the Division. We request the recommendations for the carton labeling and container label in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Maria Wasilik, at 301-796-0567.

### 3.1 COMMENTS TO THE DIVISION

#### A. GENERAL COMMENTS

1. The Applicant currently presents the established name as (testosterone solution), with the dosage form enclosed within the parenthesis throughout the labels and labeling. Per the CMC reviewer, the presentation of the established name should be (Testosterone) followed by the dosage form.
2. DMEPA is concerned whether excessive overfill of testosterone, a schedule III controlled drug substance, may increase the risk of exposure to unintended persons during the disposal process. The total drug content of the containers is proposed to be 110 mL; however, the multi-dose pump is capable of dispensing 90 mL. We defer the determination of appropriate overfill to the CMC reviewer.

#### B. HIGHLIGHTS OF PRESCRIBING INFORMATION

1. Dosage and Administration Subsection
  - a) DMEPA is concerned that the proposed dose expression does not adequately convey the necessary information to ensure the proper dose is administered. We recommend revising all Axiron dose expressions to reflect the milligrams of testosterone and appropriate number of pump actuations such as 60 mg (2 pump actuations). As currently presented, the recommended starting dose is expressed as [REDACTED] (b) (4) [REDACTED]. However, the milligrams of testosterone, not milliliters of solution, along

with the number of pump actuations are key pieces of information that healthcare providers need to communicate to the individual administering Axiron, whether it's the patient or a caretaker. Thus, including the milligrams of testosterone along with the number of pump actuations may minimize the risk associated with calculation or conversion of the number of milligrams of testosterone to the corresponding number of pump actuations. Currently there are approved medication products dispensed with metered dose devices that provide a specific amount of drug per actuation, for example asthma inhalers or nasal sprays. These products are typically dosed in terms of number of actuations, which is easier to comprehend for patients and caretakers.

- b) There is currently missing information regarding proper administration of Axiron. We recommend adding the following statement to the end of the first bulleted statement: "Apply the first pump actuation once to the left armpit and then apply the second pump actuation once to the right armpit."
- c) DMEPA is concerned that healthcare providers may attempt to interchange available topical testosterone products based upon comparison of milligrams of product or percentage strength. We recommend adding the following statement: "Testosterone topical products are not interchangeable. Prescribers should consult the Full Prescribing Information for dosing recommendations." Axiron will be the first testosterone solution approved; however, it is not the first testosterone product to be packaged in a metered dose pump. Therefore, we anticipate that healthcare providers may perceive various topical testosterone products to be interchangeable due to the following factors: same active ingredient (testosterone), same route of administration (topical), similar metered dosing devices, and similar strength designations (%).

## 2. Dosage Forms and Strengths Subsection

As currently presented, the statement (b) (4) may be confusing. We recommend changing the statement to read "1 metered-dose pump" (b) (4)

## C. FULL PRESCRIBING INFORMATION

### 1. Section 2 - Dosage and Administration

- a) See comments B(1)(a) and (B)(1)(c) above.
- b) In keeping with our rationale from B(1)(a) above, we recommend revising the table so the daily prescribed dose in the first column only reflects milligrams of testosterone. Remove any reference to milliliters of solution from the table.
- c) DMEPA is concerned that axillary hair may affect the proper dosage and administration of Axiron. We note that there are currently no instructions regarding whether shaving and/or waxing of armpits is required while using Axiron. We defer to the medical reviewer for the determination of proper instruction regarding shaving and/or waxing while using Axiron.
- d) DMEPA is uncertain whether the use of soap for cleaning the applicator is specifically contraindicated. We recommend a clear statement within the insert labeling regarding the use of soap for cleaning the applicator (e.g. Do NOT use soap to clean the applicator

after use). We defer to the medical reviewer for determination of whether a specific contraindication exists. As currently presented, there is only a single statement indicating the applicator should be rinsed under room temperature, running water and then patted dry with a tissue.

- e) DMEPA recognizes the Applicant states patients may use deodorant or antiperspirant before or after applying Axiron. However, we see in section 14.3 that Axiron and deodorant/antiperspirant use was evaluated in clinical trials with females even though Axiron is seeking approval for male patients only. Additionally, we recognize that one specific study was conducted using a 1% testosterone formulation rather than the 2% formulation that represents the final Axiron formulation. We defer to the medical reviewer for determination of appropriateness of currently proposed recommendations regarding the use of deodorant or antiperspirant with Axiron.

## 2. Section 17 – Patient Counseling Information

Under 17.4, we recommend adding the following two statements: “When using a new Axiron bottle for the first time, prime the pump by depressing the pump three times, discard any product dispensed directly into a basin, sink or toilet and then wash the liquid away thoroughly. It is not necessary to prime the pump ever day” and “When repeat application to the same armpit is required, the armpit area should be allowed to dry before more Axiron is applied.”

## D. PATIENT LABELING

1. See comments B(1)(a) above.
2. See comment C(1)(b) above. Additionally, we defer to DRISK to determine whether this dosing information is appropriate as part of the patient package insert or should be moved to instruction for use labeling.
3. The current directions for cleaning the applicator are unclear. DMEPA believes there is a typo within the statement that can be clarified to the following: “After you have finished applying AXIRON, clean the applicator by rinsing it under room temperature, running water, and then pat it dry with a tissue.” See also comment C(1)(d) above.

## 3.2 COMMENTS TO THE APPLICANT

### GENERAL COMMENTS FOR LABELS AND LABELING (2%)

1. As currently presented, 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.
2. As currently presented, 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.

3. 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.
4. As currently presented, the strength designation is not adequately prominent. Increase the prominence of the product strength on the container label and carton labeling.
5. Based on recommendations by the CMC reviewer, change the presentation of the established name from (Testosterone Solution) to (Testosterone) Solution throughout all labels and labeling.
6. 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.
7. 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.*
8. As currently presented, 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.
9. 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.
10. As currently presented, 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.
11. A medication guide is required for this product; therefore, ensure the following statement is clearly displayed in bold font on the principle display panel: “Dispense the enclosed Medication Guide to each patient.”
12. Ensure a lot number and expiration date is included on the container label and carton labeling, preferably not on the principle display panel to minimize crowding.
13. We recognize the bottle is unit-of-use for this product. Please ensure the bottle utilizes a child-resistant closure to comply with the Poison Prevention Packaging Act of 1970.

**Appendix A: Retail Container Label (front panel and back panel)**

(b) (4)



**Appendix B: Retail Carton Labeling**

(b) (4)



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

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/s/

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IRENE Z CHAN  
06/03/2010

MELINA N GRIFFIS  
06/04/2010

DENISE P TOYER  
06/04/2010

CAROL A HOLQUIST  
06/04/2010

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

Application Information		
NDA # 022504 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Axiron Established/Proper Name: testosterone solution 2% Dosage Form: solution Strengths: 2%		
Applicant: Acrux Pharma Pty. Ltd Agent for Applicant (if applicable): Kendle International		
Date of Application: January 25, 2010 Date of Receipt: January 25, 2010 Date clock started after UN:		
PDUFA Goal Date: November 25, 2010 (Thursday, Thanksgiving Day)		Action Goal Date (if different): November 24, 2010
Filing Date: March 26, 2010 Date of Filing Meeting: March 10, 2010		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed Indication(s): Treatment of hypogonadism		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>Refer to Appendix A for further information.</i></b>		
Review Classification:  <b><i>If the application includes a complete response to pediatric WR, review classification is Priority.</i></b>  <b><i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i></b>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> N/A Resubmission after refuse to file? <input type="checkbox"/> N/A		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (if OTC product): N/A	
List referenced IND Number(s):	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  <b>If yes, explain:</b>  <b>If yes, has OC/DMPQ been notified of the submission?</b>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  <b>Comments:</b>	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</p> <p>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</p> <p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	<p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
<p><b>If yes, please list below:</b></p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
<b>Format and Content</b>			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>			
<p><b>If electronic submission:</b>  paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  (<a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>)</p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b> Consult sent on March 25, 2010</p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<p>N/A</p> <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: Debarment Certification should use wording in FD&amp;C Act section 306(k)(l) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<p><b>PREA</b></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul> <p><b>Comments:</b></p>	<p><b>This product does not trigger PREA</b></p> <p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<p><b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<p>N/A</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<b>Prescription Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> <b>Not applicable</b>  <input checked="" type="checkbox"/> Package Insert (PI)  <input checked="" type="checkbox"/> Patient Package Insert (PPI)  <input type="checkbox"/> Instructions for Use  <input type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Carton labels  <input checked="" type="checkbox"/> Immediate container labels  <input type="checkbox"/> Diluent  <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b> Consult sent on March 25, 2010</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b> The consult will be sent at a later date</p>	<p><input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable at this time  <input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p><b>Comments:</b> Consult sent on March 25, 2010</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** March 25, 2010

**NDA/BLA #:** 022504

**PROPRIETARY/ESTABLISHED NAMES:** Axiron

**APPLICANT:** Acrux Pharma Pty Ltd

**BACKGROUND:** Axiron is a non-sterile, transdermally applied solution for testosterone replacement therapy in hypogonadal men. Axiron delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300- 1050 ng/dL) in healthy adult men. Axiron is administered once daily to the axilla or armpit by use of an applicator.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannie Roule	Y
	CPMS/TL:	Jennifer Mercier	N
Cross-Discipline Team Leader (CDTL)	Suresh Kaul		Y
Clinical	Reviewer:	Donald McNellis	Y
	TL:	Suresh Kaul	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:	N/A	
	TL:		
OSE	Reviewer:	Irene Chan (DMEPA)	N
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Chongwoo Yu	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jeffrey Bray	Y
	TL:	Lynnda Reid	Y
Statistics, carcinogenicity	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Hitesh Shroff	Y
	TL:	Donna Christner	Y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:	N/A	
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:	Robert Mello	Y
	TL:	James McVey	N
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	Y
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<b>Electronic Submission comments</b>  <b>List comments:</b> None	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?   <b>If no</b>, explain:</li> </ul>	<input checked="" type="checkbox"/> YES. Request for Clinical Pharmacology (pivotal clinical and bioanalytical) Sites Inspection. <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?   <b>Comments:</b>   <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul> </li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?   <b>Comments:</b></li> </ul>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed? <b>They include a clinical site as well</b></li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<b>PRODUCT QUALITY (CMC)</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <ul style="list-style-type: none"> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> George Benson</p> <p><b>GRMP Timeline Milestones:</b> Mid-cycle meeting: 06/25/10  6 month review: To be scheduled  PeRC meeting: PREA does not apply  7 month review: To be scheduled  8 month review: To be scheduled  9 Label meeting #1: To be scheduled  Label meeting #2: To be scheduled  All discipline reviews should be in DARRTS by October 31  Suresh Kaul's final review will be given to George Benson by November 11, 2009</p> <p><b>Comments:</b></p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<p><input type="checkbox"/></p>	<p>The application is unsuitable for filing. Explain why:</p>
<p><input checked="" type="checkbox"/></p>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<p><input checked="" type="checkbox"/></p>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<p><input type="checkbox"/></p>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>

<input type="checkbox"/>	
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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

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/s/

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JEANNIE M ROULE  
04/09/2010

JENNIFER L MERCIER  
04/09/2010

# DSI CONSULT: Request for Inspections – Clin Pharm

**Date:** March 18, 2010

**To:** Dr. C. T. Viswanathan, Associate Director  
Division of Scientific Investigations  
Office of Compliance, CDER  
WO Bldg 51, Room 5346  
FDA

**Through:** Chongwoo Yu, Ph.D.  
Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3 (DCP3),  
Office of Clinical Pharmacology (OCP)

Myong Jin Kim, Pharm.D.  
Clinical Pharmacology Team Leader, DCP3, OCP

Dennis Bashaw, Pharm.D.  
Director of DCP3, OCP

**From:** Jeannie Roule, Regulatory Project Manager, DRUP

**Subject:** **Request for Clinical Pharmacology (pivotal clinical and bioanalytical) Sites  
Inspection**

## **I. General Information**

Application#: NDA 22-504

Acrux Pharma Pty Ltd.  
Attention: Michelle Wilson, US Agent  
Kendle International Inc.  
441 Vine St., Suite 500  
Cincinnati, OH 45202  
Ph: 1-513-829-1108  
Email: wilson.michelle@kendle.com

Drug Proprietary Name: Axiron (Testosterone solution, 2%)  
NME or Original BLA: No  
Review Priority: Standard

Study Population includes < 17 years of age: No  
Is this for Pediatric Exclusivity: No

Proposed New Indication(s): Treatment of hypogonadism

PDUFA:  
Action Goal Date: November 25, 2010

DSI Consult  
January 30, 2009

Inspection Summary Goal Date: August 9, 2010

**II. Protocol/Site Identification**

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID <sup>a</sup>	Number of Subjects	Indication
Regional Urology 255 BERT Kouns, Shreveport, LA 71105 Phone: 318-683-0411(x-154) <i>Clinical site #205</i>  Deerfoot Internal Medicine 6725 Deerfoot Parkway, Birmingham, AL 35126 Phone: 205-681-0352 <i>Clinical site #207</i>  Northwest Clinical Trials 7149 West Emerald Street, Boise, ID 83704 Phone: 208-685-0600 <i>Clinical site #211</i>	MTE08, MTE09	For both Studies MTE08 and MTE09 - Clinical site #205: 13 Clinical site #207: 13 Clinical site #211: 13	Treatment of hypogonadism
(b) (4)	MTE07, MTE08, MTE09, MTE10, MTE11 <sup>b</sup>	MTE07: 21 MTE08: 155 MTE09: 52 MTE10: 36 MTE11: 10-12 (MTE11 - ongoing)	Treatment of hypogonadism
(b) (4)	MTE06	96	Treatment of hypogonadism

<sup>a</sup> For description of each study, please refer to the Table in the Appendix.

<sup>b</sup> Sponsor has informed the Division about their plan of providing the final report for Study MTE11 in March/April 2010. Therefore, it appears that the study should have been completed by now.

**III. Site Selection/Rationale**

The selected clinical sites are the sites that have the most significant population enrolled for the pivotal Phase 3 safety and efficacy study (MTE08 and MTE09 [extended safety substudy]). (b) (4) bioanalytical site analyzed all the study samples conducted using the to-be-marketed (TBM) formulation including the pivotal Phase 3 study samples. (b) (4) bioanalytical site (b) (4) analyzed the samples obtained from Study MTE006 including the transfer study that is critical information. In addition, (b) (4) had some critical deficiency history in the past regarding compliance with Good Laboratory Practices (GLP). Therefore, DSI inspection is warranted.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):

- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): In addition, one of the bioanalytical sites has critical deficiency history regarding compliance with Good Laboratory Practices (GLP).

**International Inspections:**

Reasons for inspections (please check all that apply): NA

- There are insufficient domestic data
- Only** foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

*If you have specific data that needs to be verified, please provide a table for data verification, if applicable.*

Should you require any additional information, please contact Jeannie Roule at 301-796-3993.

Concurrence: (as needed)

\_\_\_\_\_ Medical Team Leader  
 \_\_\_\_\_ Medical Reviewer  
 \_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**Additional Information:**

The investigational product (Axiron) is non-sterile, transdermally applied solution for testosterone replacement therapy in hypogonadal men. Axiron delivers physiologic amounts of testosterone, aiming to produce circulating testosterone concentrations that approximate normal levels (300 – 1050 ng/dl) in healthy adult men. Axiron is administered transdermally once daily to clean, dry intact skin of the axilla or armpit (not to any other parts of the body) by use of an applicator, preferably at the same time each morning following showering. The product is applied via a metered-dose pump designed to deliver 1.5 ml of the formulation to an applicator which is then used to apply the product to the skin of the axilla. The recommended start dose is 3 ml (60 mg of testosterone).

Serum study samples were analyzed for total testosterone and dihydrotestosterone (DHT). In Study MTE06, testosterone was measured by a liquid chromatography–tandem mass spectrometry (LC-MS/MS) method at (b) (4). DHT was measured by radioimmunoassay (RIA) after extraction and oxidation. LC-MS/MS methods were used in all other studies (MTE07, MTE08, MTE09, and MTE10) and bioanalysis for these study samples were conducted at (b) (4)

## Appendix

Clinical Studies subject to DSI Consult Request:

Type of Study	Study Identifier	Objectives of the Study	Study Design and Type of Control	Test Product(s)	N	Type of Subjects	Study Status; Type of Report	Location of Report
PK	MTE07	Compare steady state PK of different doses and formulations of Testosterone MD-Lotion (1% and 2%).	Randomized 4-way crossover	Axillary application of 30mg and 60 mg of 1% and 2% Testosterone MD-Lotion®	21	Hypogonadal Males	Complete; Legacy CSR	<a href="#">5.3.5.2</a>
Efficacy and Safety	MTE08	Confirm efficacy and safety of Testosterone MD-Lotion 2%	Open label titration	Dermal application of 30 mg applied to 1 axilla once, 60 mg daily to both axilla, 90 mg x 3, and 120 mg x 4 (2% testosterone) Testosterone MD-Lotion®.	155	Hypogonadal Males	Complete; CSR with eCTD granularity	<a href="#">5.3.5.2</a>
Safety	MTE09	Assess skin safety of continuous use of the Testosterone MD-Lotion® 2% after completion of the MTE08 trial	Open label titration	Dermal application of 30 mg applied to 1 axilla once, 60 mg daily to both axilla, 90 mg x 3, and 120 mg x 4 (2% testosterone) Testosterone MD-Lotion®.	52	Hypogonadal Males		
Safety	MTE10	Evaluate impact of washing and deodorant or antiperspirant use on absorption.	Randomized, single dose, parallel group design.	Testosterone MD Lotion® containing 2 % testosterone.	36	Healthy Females	Complete; Legacy CSR	<a href="#">5.3.5.4</a>
Safety	MTE11	Evaluate the impact of washing on absorption.	Open label, single-dose	Testosterone MD-Lotion containing 2% testosterone	10-12	Healthy Volunteers	Planned	N/A
Safety	MTE06	Evaluate transfer to female partners, impact of washing and deodorant or antiperspirant use on absorption	Randomized, open-label, 3 part study design in normal, healthy, male and female subjects.	Single Axillary Application: Part A/Transfer: 6 ml Testosterone MD-Lotion® Parts B and C/Effect of Deodorant and Antiperspirant and Washing: 3ml Testosterone MD-Lotion® to one axilla	96	Part A: 24 Healthy Males/24 Healthy Females Part B:24 Healthy Females Part C:24 Healthy Females	Complete; Legacy CSR	<a href="#">5.3.5.4</a>

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

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/s/

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JEANNIE M ROULE  
03/18/2010

EDWARD D BASHAW  
03/18/2010