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APPLICATION NUMBER:

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SUMMARY REVIEW

Deputy Division Director Summary Review for Regulatory Action

Date	November 23, 2010
From	George S. Benson, MD
Subject	Division Deputy Director Summary Review
NDA/BLA #	22-504
Applicant Name	Acrux Pharma Pty Ltd
Date of Submission	January 25, 2010
PDUFA Goal Date	November 25, 2010
Proprietary Name / Established Name	Axiron Testosterone solution
Dosage Forms / Strength	Testosterone solution for transdermal use/2% testesterone
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action	Approval

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Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Jeffrey Bray, PhD Lynnda Reid, PhD
CMC Review	Hitesh Shroff, PhD Donna Christner, PhD Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Chongwoo Yu, PhD Myong Jin Kim, PharmD
CDTL Review	Suresh Kaul, MD
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OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
SEALD = Study Endpoints and Labeling Development

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1. Introduction

NDA 22-504 for Axiron (2% testosterone solution) for the indication testosterone "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone" was submitted on January 25, 2010. Testosterone for replacement therapy in men is currently available in a variety of dosage forms and routes of administration including intramuscular injection, testosterone implants, buccal tablets, and transdermal patches and gels. Axiron differs from currently approved testosterone replacement products in that it is a testosterone solution and is applied to the axillae with an applicator. The applicator is filled with testosterone solution delivered by a pump.

The transfer of testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. An Advisory Committee meeting regarding this issue was held on June 23, 2009. Both AndroGel and Testim (both testosterone gel products) currently have black box warnings and Medication Guides relating to the increased awareness of secondary exposure of children to testosterone gels. Transfer of testosterone to others is also a safety concern with Axiron.

2. Background

IND 70,516 (testosterone 2% solution) was submitted to the Division of Reproductive and Urologic Products on August 11, 2006, by Acrux Pharma. An end-of-phase 2 meeting between Acrux and the Division was held on March 13, 2008. At this meeting, the design of Acrux's planned phase 3 study was discussed, including the dose titration scheme, the primary and secondary endpoints and the safety monitoring for the trial.

Prior to this meeting, Acrux had completed studies evaluating the effect of deodorant use, application site washing, and person-to-person transfer. These initial studies had been conducted using a 1% formulation of the product rather than the 2% formulation that the Sponsor intends to market. This change in formulation was discussed and the Division indicated that, while it is unlikely that these trials would need to be repeated using the

new formulation, a final decision would only be possible after review of the study reports.

On August 31, 2009, a pre-NDA meeting was held. The need for a clinical study evaluating the ability of soap and water to remove the product from the skin was discussed.

During the review, the review team believed that the absence of a study evaluating person-to-person transfer using the to-be-marketed formulation (2% testosterone) was a significant deficiency. The transfer study (MTE11) that was submitted with the NDA application evaluated a 1% solution. This was discussed with the Sponsor who agreed to perform the necessary study. The Sponsor submitted this study report, MTE12, during the NDA review cycle.

3. CMC/Device

The chemistry review concluded that "this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. The labels have adequate information as required. An "Acceptable" site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is recommended for approval."

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review concluded that "nonclinical data support approval of testosterone 2% solution for topical (axilla) testosterone replacement in hypogonadal men."

Two issues arose with characterization of the drug product. "A red coloration noted in the accelerated stability registration batches was investigated by the sponsor and the source was found to be specific to (b) (4) povidone (b) (4) It was not isolated or identified, suggesting that it was present only in trace amounts. Since the red color-causing species is only present at trace levels under accelerated conditions, and a likely source has been identified and can be eliminated through CMC specifications, the impurity's presence in the registration batches does not affect approval of this product from a Pharm/Tox perspective. Dimethicone oil from the pump was detected in drug product following the first few pump actuations. The ubiquitous presence of dimethicone in cosmetics, in the clinical batch, and its known low dermal toxicity represents a low human safety risk in the testosterone 2% solution."

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review stated that "the overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language."

The review further states that "DSI's memorandum reveals that there are no unresolved issues that would affect the approvability of Axiron (refer to DSI's memorandum in DARRTS dated October 29, 2010)."

An amended Clinical Pharmacology review was completed on November 22, 2010 and included:

A discussion of the reasons why, from a clinical pharmacology perspective, the deficiencies found during the DSI inspection of the bioanalytical sites do not affect clinical pharmacology's final recommendation on product approval.

The overall Clinical Pharmacology recommendation on product labeling states: "The final agreed upon product labeling between the Sponsor and the DRUP was submitted by the Sponsor on November 19, 2010. There are no outstanding Clinical Pharmacology issues."

The final Clinical Pharmacology recommendation states: "The Division of Clinical Pharmacology 3, OCP finds NDA 022504 acceptable from a Clinical Pharmacology Perspective."

The clinical review team/cross discipline team leader and the clinical pharmacology review team did not agree on labeling issues relating to Section 14 (Clinical Studies section) of the label. I agree with the format/content of the tables and figures in this section of the label as proposed by the clinical review team/cross discipline team leader.

6. Clinical Microbiology

The Application was "recommended for approval from a microbiology product quality standpoint."

7. Clinical/Statistical-Efficacy

Data to support efficacy are derived primarily from clinical trial MTE08. Trial MTE08 was a Phase III open-label titration trial to evaluate the effectiveness and safety of a dermal application of Axiron in hypogonadal men. The study was carried out at 25 sites in Australia, France, Germany, Sweden, the United Kingdom and the United States.

Inclusion/exclusion criteria:

Inclusion criteria included:

- Male subjects greater than 18 years of age with a prior documented definitive diagnosis of hypogonadism as evidenced by previously documented:
    - Hypothalamic, pituitary, or testicular disorder or age related idiopathic hypogonadism, and
    - Screening serum testosterone of ≤ 300 ng/dL (based on the average of two morning samples taken at least 30 minutes apart),
- Body Mass Index (BMI) < 35.0 kg/m^2

Exclusion criteria included:

- Chronic skin disorder (e.g. eczema, psoriasis) likely to interfere with transdermal drug absorption
- Any man in whom testosterone therapy was contraindicated, which included those with:
    - Known or suspected carcinoma (or history of carcinoma) of the prostate or clinically significant symptoms of benign prostatic hyperplasia and/or clinically significant symptoms of lower urinary obstruction and IPSS scores of ≥ 19
    - Known or suspected carcinoma (or history of carcinoma) of the breast
    - Severe liver disease (i.e. cirrhosis, hepatitis or liver tumors or liver function tests >2 times the upper limit of the normal range values)
    - Active deep vein thrombosis, thromboembolic disorders or a documented history of these conditions
    - Current significant cerebrovascular or coronary artery disease,
    - Untreated sleep apnea
    - Hematocrit of > 51
    - Untreated moderate to severe depression
- Men with clinically significant abnormal prostate examination or clinically significant elevated serum Prostate Specific Antigen (PSA) levels (> 4 ng/mL), or age adjusted reference range of PSA values

Treatment regimen:

The initial dose of Axiron was 3ml (60mg) administered as 1.5 ml to each axilla once daily.

On day 15 and again on day 60, subjects underwent 24 hour pharmacokinetic evaluation which allowed calculation of C_{avg} testosterone concentration. On day 45 and day 90 the Axiron dose was titrated according to the following:

- If C_{avg} were in the normal range (300 – 1050 ng/dL), the dose was not changed.
- If C_{avg} were <300 ng/dL, the dose was increased by 30 mg to 90 mg or 120 mg.
- If C_{avg} were >1050 ng/dL, the dose was decreased by 30 mg. If the dose had previously been decreased to 30mg, the patient was discontinued from the trial.

Clinic visits occurred at baseline and on days 15, 45, 60, 90 and 120. For subjects continuing into extension study MTE09, final physical examination and laboratory evaluation occurred at the completion of that study rather than on day 120 of study MTE08.

Efficacy Endpoints:

Primary Endpoint

The primary efficacy endpoint for Trial MTE08 was C_{avg} for total testosterone in the defined normal range (300-1050 ng/dL). As agreed upon with the Division, the product would be considered to have achieved this endpoint if ≥75% of subjects, with the lower bound of the 95% confidence interval >66.8%, had C_{avg} within this range on day 120.

Secondary Endpoints:

The following were included in multiple secondary efficacy endpoints which were evaluated:

- The proportion of subjects with total testosterone C_{max} <1500 ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if >85% of subjects had C_{max} <1500 ng/dL on day 120.
- The proportion of subjects with total testosterone C_{max} between 1800 ng/dL and 2500 ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if <5% of subjects had C_{max} in this range on day 120.
- The proportion of subjects with total testosterone C_{max} >2500 ng/dL. As agreed upon with the Division, the product would be considered to have achieved this endpoint if no subjects had C_{max} >2500 ng/dL on day 120.

The final doses of Axiron (following titration) are shown in Table 1.

Table 1: Study Participants by Final Testosterone Dose

	MTE08				MTE09
Maintenance Dose of Testosterone Solution	Safety Set[1] N(%)	Full Analysis Set[2] N(%)	Completer Set[3] N(%)	Per Protocol Set[4] N(%)	Safety Set N(%)
30 mg	3 (1.9)	3 (2.1)	3 (2.2)	3 (2.4)	2 (2.8)
60 mg	117 (75.5)	105 (73.4)	100 (72.5)	88 (71.5)	49 (69.0)
90 mg	25 (16.1)	25 (17.5)	25 (18.1)	22 (17.9)	12 (16.9)
120 mg	10 (6.5)	10 (7.0)	10 (7.2)	10 (8.1)	8 (11.3)
Overall	155 (100.0)	143 (100.0)	138 (100.0)	123 (100.0)	71 (100.0)

Source: NDA 22504 submission, Module 5.3.5.2, Table 14.1.1.2
[1] Safety Set = Any subject who entered the study and received at least one dose of investigational product.
[2] Full Analysis Set = All subjects who entered the trial, received at least one dose of investigational product, and have on-treatment data for at least one efficacy variable.
[3] Completer Set = All subjects in the Full Analysis Set who also completed the Day 120 Visit. Subjects who withdrew prior to Day 120 due to either lack of efficacy or an adverse event will also be included in the Completer Set.
[4] Per Protocol Set = All subjects who completed the trial without any significant protocol deviations or violations.

85.8% of the safety set cohort patients had at least one prior treatment for hypogonadism. Only 14.2% of the study population was naïve to testosterone therapy.

Subject Disposition:

One hundred fifty-five subjects were enrolled in study MTE08. Twenty subjects were subsequently withdrawn from the study. The reasons for withdrawal are shown in Table 2.

Table 2. Reasons for Withdrawal from Study MTE08

Reason for Withdrawal	Number of Subjects
Withdrew consent	9
Non-compliance with study drug	3
Lost to follow-up	2
Non-compliance with site directives	1
Sponsor request	1
Screening Testosterone level >300 ng/dL	1
AE: Superficial thrombophlebitis	1
AE: Melanoma of scalp	1
AE: Emotional changes	1

Source: NDA 22504 submission, Module 5.3.5.2, Table 10-1

Three patients were withdrawn because of an adverse event. The emotional changes leading to withdrawal were judged to be possibly related to study drug. The phlebitis and melanoma were believed to be unrelated.

Analysis of Primary Endpoint:

The primary assessment of efficacy, as specified at the end-of-phase 2 meeting, was based on the proportion of subjects with C_{avg} (0-24h) total testosterone within the normal range (300 – 1050 ng/dL) on day 120 of the trial. In order to be considered an effective treatment, this proportion was pre-defined to be ≥75%, with the lower bound of the 95% confidence interval > 66.8%. The proportion of subjects having C_{avg} total testosterone within the normal range at three time points is shown in Table 3.

Table 3. Proportion of Subjects with Serum Total Testosterone C_{avg} in the Range of 300 – 1050 ng/dL (Percent, 95% CI, N)

Data Set	Day 15/16	Day 60/61	Day 120/121
Completer Set (N=138)	76.1% (69.0 – 83.2) 105/138	84.8% (78.8 – 90.8) 117/138	84.1% (78.0 – 90.2) 116/138
Full Analysis Set (N=143)	77.6% 111/143	86.2% 119/138	84.1% 116/138

Source: NDA 22504, Module 5.3.5.2, Table 11-1, page 92.

The primary endpoint based on testosterone C_{avg} is the endpoint currently used in the evaluation of all testosterone products submitted for the indication of testosterone replacement therapy. The values obtained for Axiron are within the accepted ranges and the primary endpoint has been met.

The data for four of the secondary endpoints that are based on pharmacokinetic data are shown in Table 4.

Table 4. Secondary Serum Total Testosterone Pharmacokinetic Endpoints (Completer Set)

Data	Target	Day 15/16	Day 60/61	Day 120/121
C_{max} < 1500 ng/dL	> 85%	95.6% 130/136	91.2% 124/136	94.5% 128/135
C_{max} > 2500 ng/dL	0	1.5% 2/136	1.5% 2/136	0.7% 1/135
C_{max} >1800 and ≤ 2500 ng/dL	< 5%	2.2% 3/136	4.4% 6/136	3.0% 4/135
C_{min} < 300 ng/dL	No prespecified Target value	71.3% 97/136	69.1% 94/136	64.4% 87/135

Source: NDA 22504, Module 5.3.5.2, Table 11-2, page 93

These secondary pharmacokinetic endpoints are considered to be "safety endpoints" to ensure that patients are not exposed to excessively high testosterone serum concentrations. The proportion of subjects with testosterone C_{max} less than 1500 ng/dL and the proportion of subjects with testosterone C_{max} between 1800 ng/dL and 2500 ng/dL in trial MTE08 are within current Division guidelines.

Five patients, however, had a C_{max} value >2500 ng/dL at some point during the study. Currently, the Division believes that no patient should have a C_{max} in this range. These elevated testosterone levels are shown in Table 5.

Table 5. Subjects with Serum Total Testosterone C_{max} >2500 ng/dL at any time point

Subject	C_{max} (ng/dL)	T_{max} (hours)	pK Sampling Day
21134	4280	8	Day 15
21139	3247	12	Day 15
21108	2554	8	Day 60
20101	5996	2	Day 60
20504	3457	8	Day 120

Source: NDA 22504, Module 5.3.5.2, Table 11-3, page 94

An analysis of the pharmacokinetic data for the five subjects shows that, in four of the five, the elevated value is a single point that appears to be inconsistent with respect to the data points on either side of it. In two of the four subjects, 21134 and 21108, the testosterone elevation was not accompanied by any significant elevation of DHT. This suggests that in these subjects the testosterone elevation was likely secondary to contamination of the blood sample. The application site could well have included the area where the venipuncture was performed. After review of each of the individual cases, the primary medical officer concluded (see pages 43-47 of the Primary Medical Officer review) that four of the five elevations could be reasonably ascribed to contamination of the specimen by testosterone on the skin. In the fifth case (subject # 21139) the primary medical officer concluded that the sustained testosterone concentration was likely a true elevation of >2500 ng/dL. This elevation occurred, however, on Day 15 prior to down

titration. No subsequent post-titration elevated testosterone values were seen in this patient.

Two variables that may affect efficacy were further evaluated: 1) the effect of underarm deodorant use and 2) the effect of washing the application site. The effects of deodorant use and washing were evaluated in a dedicated trial (MTE10) and also by means of subgroup analyses of subjects in primary efficacy and safety trial MTE08. The numbers of subjects enrolled in trial MTE10 were relatively small. In the antiperspirant/deodorant phase of the trial, lower serum levels of testosterone (by approximately 33%) were seen in patients who applied antiperspirant/deodorant two minutes prior to the testosterone application. The subgroup analyses from trial MTE08 indicate that at day 120 there was no evidence that the use of an antiperspirant or deodorant had a significant effect on testosterone concentration. Both the group that used deodorant every day and the group that did not ever use deodorant satisfied the criteria of having >75% within the normal range with the lower bound of the 95% CI > 66.8%.

With respect to washing the application site, trial MTE10 showed that washing the site either 2 hours or 6 hours post testosterone application did decrease serum testosterone levels. In Study MTE08, subjects were asked whether they showered or washed during the 24 hour period following application of testosterone solution on days 15, 60 and 120, i.e., did they wash while the 24 hour PK profile was being determined. The data show that showering or washing the application site did not adversely affect the efficacy of the product, i.e., the response rate (proportion of patients with C_{avg} in the normal range) for those who washed the application site (two hours or more after dosing) during the 24 hour intensive PK sampling was not significantly different from those that did or from the overall response rate.

After reviewing these data, the Primary Medical Officer and the Clinical Pharmacology reviewer concluded that neither antiperspirant/deodorant use nor washing after two hours significantly influenced testosterone levels and I agree. These data can be labeled.

During Study MTE08, all dose titration decisions were made based on C_{avg} of total testosterone values. In clinical practice, dose titration decisions are made based on single values of total testosterone concentration. The Sponsor provided an analysis of the data from Study MTE08 to assess the relationship between single testosterone concentration values done at various times after dose application and the eventual 24 hour C_{avg} values. After reviewing these data, the Primary Medical Officer and the Clinical Pharmacology reviewer agreed with the Sponsor's recommendation for titrating the dose based on a single testosterone value drawn 2 – 8 hours after application of the product. The single testosterone levels obtained during this timeframe appear to support a decision for titration which correlate with C_{avg} values while minimizing the likelihood of titration to a dose higher than one that was based on C_{avg} values. A single value drawn at 4 hours after application appears to be the optimum single blood draw on which to base a titration decision.

Statistical review:

The statistical reviewer concluded that "from a statistical perspective, the efficacy has been demonstrated in support of the transdermally applied 2% testosterone solution (Axiron) as testosterone replacement therapy for conditions associated with androgen deficiency."

Efficacy Summary

The Sponsor conducted one clinical trial (MTE08) evaluating the efficacy of Axiron testosterone 2% transdermal solution in producing serum testosterone levels within the normal range when the solution is used in hypogonadal men. This trial was adequately designed and evaluated accepted endpoints for the evaluation testosterone products. The prespecified endpoints were met.

In addition, the Sponsor conducted a clinical trial (MTE10) which evaluated the effect of underarm deodorant use and the effect of application site washing on product efficacy. This study, together with Study MTE08, indicates that, while deodorant use or washing the application site lowers the testosterone exposure, no adverse effect on overall efficacy was seen.

8. Safety

The primary safety database consists of primary phase 3 trial MTE08 (three month study) and its extension study MTE09 (additional 3 months of exposure).

Exposure:

Table 6 shows the number of patients with exposure to Axiron in Studies MTE08 and MTE09.

Table 6. Exposure to Testosterone Solution – Studies MTE08 and MTE09

	Number of Patients With Exposure to Solution for			
Dose	≥30 Days	≥90 Days	≥120 Days	≥180 Days
Any Dose	149	147	134	51
30 mg/Day	3	2	0	0
60 mg/Day	137	107	97	40
90 mg/Day	34	8	5	0
120 mg/Day	9	3	0	0

Source: MO Analysis of Module 5.3.5.2.25.3.1, Analysis Dataset ADSL

Demographics:

The demographics of the study population for studies MTE08 and MTE09 are shown in Table 7.

Table 7. Demographics - Studies MTE08 and MTE09

	Maintenance Dose of Testosterone Solution				
	All Doses N=155	30 mg N=3	60 mg N=117	90 mg N=25	120 mg N=10
Age					
Mean	51.5	57.3	51.3	52.9	48.7
Range	19 – 78	51 – 65	19 – 78	25 – 75	30 – 62
Race					
Asian	1 (0.7%)	0	1 (0.9%)	0	0
Caucasian	122 (84.7%)	2 (66.7%)	94 (86.2%)	19 (86.4%)	7 (70%)
African American	6 (4.2%)	0	2 (1.8%)	3 (13.6%)	1 (10.0%
Hispanic	13 (9.0%)	1 (33.3%)	10 (9.2%)	0	2 (20.0%)
Other	2 (1.4%)	0	2 (1.8%)	0	0
Weight (kg)					
Mean	94.4	83.4	94.5	94.6	95.1
Range	59.1 – 126.1	79.4 – 90.3	59.1 – 126.1	75.5 – 119.7	75.9 – 123.6
BMI (kg/m^2)					
Mean	29.5	28.1	29.6	29.7	29.1
Range	18.2 – 38.9	24.8 –34.4	18.2 – 38.9	24.6 – 35.0	23.9 – 34.8

Source: Module 5.3.5.2.3, Table 14.1.2.1

The subjects requiring only a 30 mg/day dose of testosterone are lighter in weight and have a lower BMI than other subjects. Overall, the demographics of the study population appear to be representative of the target population.

Deaths:

There were no deaths during the clinical studies evaluating this product.

Nonfatal Serious Adverse Events (SAE's):

The serious adverse events reported during studies MTE08 and MTE09 are shown in Table 8. There were no serious adverse events reported in Phase 1 and Phase 2 studies.

Table 8. Serious Adverse Events

Study	Subject Number	Testosterone Dose	Event (Medra PT)
MTE08	20203	120 mg	Appendicitis
MTE08	20530	90 mg	Scalp Melanoma
MTE09	20711	60 mg	Hepatitis C
MTE09	21016	60 mg	Prostate Cancer

Source: NDA 22504, Module 5.3.5.2.3, Table 12-9

Each of these SAE's was reviewed in detail by the primary medical officer (see pages 61 to 64 of Primary Medical Officer review). The cases of appendicitis and melanoma were

judged to be not related to testosterone replacement and the case of elevated transaminases was ascribed to hepatitis C. The case of prostate cancer involved a 55-year-old man whose PSA at screening (October 7, 2008) was 1.3 ng/mL. He was treated with the 60 mg dose of Axiron for the entire 120 day treatment period. As part of the MTE09 "rollover" on February 24, 2009, his PSA was repeated and found to be 7.3. A repeat PSA was 6.4. Another PSA measurement on April 20, 2009 was 3.2, and the patient underwent a prostate biospsy with the finding of a Gleason 6 prostate adenocarcinoma. I agree with the opinion of the primary medical officer that this prostate cancer is not likely to be related to the testosterone administration. The testosterone therapy may have been a factor in the PSA rise which led to the diagnosis.

Study discontinuation:

Three patients discontinued trial MTE08 because of an adverse event. One had a scalp melanoma. The second had a history of varicose veins. He started study drug on January 8, 2009, and was evaluated for his varicose veins on January 9, 2009, at which time a diagnosis of superficial thrombophlebitis was made. The patient had a 20 year history of varicose veins and the investigator believed that the patient was withdrawn because of a pre-existing condition. The third patient was a 28-year-old man with a 20 year history of a seizure disorder. The subject started Day 1 of the MTE08 study on October 2, 2008. He did not return for his Day 15 visit on October 17, 2008. He informed the investigator that he had been to the Emergency Room (b) (6). He reported that within the week prior to going to the hospital he had been under stress and had "broken up" with his girlfriend. The reason for the Emergency visit was that he was angry and emotional. The subject's mother had called an emergency number because she was afraid of his behavior. He was not treated at the hospital but he was observed for several hours. He stated to the hospital personnel that he thought that the way he was feeling was due to the investigational product. The hospital staff advised him to stop the treatment. The subject reported that after two days off the investigational product he "felt better". He reported no past psychological problems. The association between the investigational product and the emotional episode can not be ruled out.

Following completion of Study MTE08, 71 subjects were enrolled in the safety extension Study MTE09. Twenty of these subjects withdrew from MTE09 (Table 9).

Table 9. Reason for Withdrawal from Study MTE09

Reason for Withdrawal	Number of Subjects
Day 120 C_{avg} outside normal range	9
Elevated Hgb or Hct	4
Elevated PSA	1
Elevated HbA1c	1
Skin reaction	2
Lost to follow up	1
Withdrew consent	2

Source: NDA 22504, Module 5.3.5.2.3, Table 10-2

Fifteen of the twenty withdrawals occurred because the subjects had blood tests that had been drawn at the Day 120 visit for Study MTE08 and showed the subject to have a value that excluded them from continuing in Study MTE09. Only two subjects discontinued because of an adverse event. Both of them were skin related. These skin reactions were mild, do not raise significant concerns, and can be adequately labeled.

Common Adverse Events:

The common adverse event data from the phase 3 primary efficacy trial, MTE08, are presented in Table 10, and the data from the safety extension study MTE09 are presented in Table 11. The most common adverse events were application site erythema/irritation/edema, increased hematocrit, headache, diarrhea, vomiting, increased PSA, and nasopharyngitis.

Table 10. Common Treatment-emergent Adverse Events (>2%) occurring in Study MTE08

Medra SOC Preferred Term	Dose of Testosterone Solution				
	30mg N (%)	60mg N (%)	90mg N (%)	120mg N (%)	Overall N (%)
Subjects with at least one TEAE	3 (75%)	71 (45.8%)	13 (37.1%)	5 (50.0%)	81 (52.3%)
Total number of TEAEs	4	177	31	8	220
General Disorders and Administrative Site Conditions					
Application site erythema	0	8 (5.2%)	0	0	8 (5.2%)
Application site irritation	0	10 (6.5%)	1 (2.9%)	1 (10%)	12 (7.7%)
Infections and Infestations					
Nasopharyngitis	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
Investigations					
Hematocrit increased	0	5 (3.2%)	1 (2.9%)	0	6 (3.9%)
Nervous System Disorders					
Headache	0	8 (5.2%)	0	0	8 (5.2%)
Gastrointestinal Disorders					
Diarrhea	0	2 (1.3%)	2 (5.7%)	0	4 (2.6%)
Vomiting	0	3 (1.9%)	1 (2.9%)	0	4 (2.6%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-3.

Table 11. Common Treatment-emergent Adverse Events (>2%) occurring in Study MTE09

Medra SOC Preferred Term	Dose of Testosterone Solution				
	30mg N (%)	60mg N (%)	90mg N (%)	120mg N (%)	Overall N (%)
Subjects with at least one TEAE	2 (66.7%)	36 (50.7%)	10 (50.0%)	4 (50.0%)	45 (63.4%)
Total number of TEAEs	6	92	23	11	132
General Disorders and Administrative Site Conditions					
Application site erythema	0	4 (5.6%)	0	1(12.5%)	5 (7.0%)
Application site irritation	0	5 (7.0%)	1 (5.0%)	0	6 (8.5%)
Application site edema	0	2 (2.8%)	0	0	2 (2.8%)
Infections and Infestations					
Fungal Infection	0	2 (2.8%)	0	0	2 (2.8%)
Herpes Zoster	0	1 (1.4%)	1 (5.0%)	0	2 (2.8%)
Upper Respiratory Infection	0	1 (1.4%)	0	1(12.5%)	2 (2.8%)
Investigations					
Hematocrit increased	0	5 (7.0%)	0	0	5 (7.0%)
PSA Increased	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Nervous System Disorders					
Headache	0	3 (4.2%)	0	0	3 (4.2%)
Gastrointestinal Disorders					
Diarrhea	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Vomiting	0	2 (2.8%)	1 (5.0%)	0	3 (4.2%)
Skin and Subcutaneous Tissue Disorders					
Dry Skin	0	0	1 (5.0%)	1(12.5%)	2 (2.8%)
Hyperkeratosis	0	1 (1.4%)	0	1(12.5%)	2 (2.8%)
Rash	0	2 (2.8%)	0	0	2 (2.8%)
Musculoskeletal and Connective Tissue Disorders					
Back pain	0	1 (1.4%)	1 (5.0%)	0	2 (2.8%)
Vascular Disorders					
Hypertension	0	2 (4.1%)	0	0	2 (2.8%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-4.

The application site events, increased hematocrit, and PSA change are reasonably likely to be drug related. Most skin reactions were mild and did not require discontinuation of medication.

A review of the adverse events seen by subjects in the phase 1 studies MTE07 and MTE11 did not reveal events that differed from those seen in studies MTE08 and MTE09.

Transfer and Washing Studies:

The issue of transfer of testosterone from a patient using a transdermal product to another individual via person-to-person transfer has been shown to be a significant safety issue with transdermal testosterone gel products. This was discussed at a Pediatric Advisory Committee meeting held on June 23, 2009. Transdermal testosterone gel product labels were revised in 2009 to incorporate a boxed warning concerning this potential transfer and a Medication Guide was required.

To evaluate the potential for interpersonal transfer, the Sponsor conducted three trials. Study MTE06 was a study evaluating person to person transfer of a 1% testosterone solution, study MTE12 evaluated a 2% testosterone solution (Axiron), and Study MTE11 evaluated the ability to wash Axiron from the skin using soap and water.

Person-to-Person Transfer – Studies MTE06 and MTE12

These studies evaluated the transfer of testosterone from male subjects, to whom the product was applied, to female subjects who had contact with the application area. The measure of transfer was the testosterone pharmacokinetics in the female subject. In study MTE06, four cohorts of subjects were evaluated, each cohort being composed of six male/female pairs. One cohort underwent 15 minutes of contact between the female's forearm and the male's axilla 2 hours after the product had been applied to the male. A second cohort had the contact at the same time, but with the male wearing a shirt. The third and fourth cohorts had the contact, without a shirt, at six hours and 12 hours after application of the product. Study MTE06 evaluated this transfer using a 1% testosterone solution. Table 12 shows study MTE06 pharmacokinetic results for total testosterone.

Table 12. Pharmacokinetics for Total Testosterone in Female Subjects Following contact with the Application Site of a Male Subject. MTE06

Parameter	Mean ± SD			
	Contact at 2 hr without shirt N=6	Contact at 2 hr with shirt N=6	Contact at 6 hr without shirt N=6	Contact at 12 hr without shirt N=6
AUC_{0-72} (ng/dL*hr)	5050 ± 2793	2135 ± 911	4790 ± 3416	5827 ± 1761
C_{MAX} (ng/dL)	225 ± 185	47 ± 26	165 ± 116	496 ± 383
C_{MIN} (ng/dL)	20 ± 5.7	23 ± 12.1	30 ± 22.0	31 ± 7.9
T_{MAX} (hr)	12	12	10	4.5

Source: NDA 22504, Module 5.3.5.4.3, Table 11.4.1.3.1.1

Because Study MTE06 was carried out using a 1% testosterone solution, the Sponsor was asked to evaluate the ability of a clothing barrier to block the transfer of the to-be-marketed 2% testosterone solution (Axiron). This was evaluated in Study MTE12.

In Study MTE12, ten male/female pairs were evaluated. The female partners had baseline testosterone pharmacokinetics evaluated with blood draws for 24 hours prior to contact. The male subject had a single 120 mg dose of 2% testosterone solution applied (60 mg to each axilla) on the day of contact. Two hours after the application, while wearing a long-sleeved cotton shirt, the partners had 15 minutes of contact between the female's forearm and the male's axilla. The female partner had blood draws for testosterone pharmacokinetics for 72 hours after the contact.

One female partner was dropped from the study for a major protocol violation – she was enrolled in another clinical study simultaneously. The results are based on an analysis of nine female subjects.

These results demonstrated that there is a significant potential for testosterone to transfer from the application site of an individual to another individual via skin-to-skin contact. However, a clothing barrier significantly reduces this transfer. Following skin to clothed application site contact, the mean testosterone values of the female subjects 24 hours following contact as compared to the 24 hours prior to contact are within the normal limits of testosterone levels for a female.

Although there is a slight increase over the baseline, the serum testosterone concentrations remained well within normal limits following this clothed contact whereas they rose above the upper limit of normal following direct skin-to-skin contact. I agree with the primary medical officer that "therefore, it is reasonable to conclude that a clothing barrier does not completely eliminate testosterone transfer, but does provide adequate protection from clinically meaningful transfer."

Washing Testosterone from the Skin – Study MTE11

This study evaluated the ability to wash testosterone from the skin. The study enrolled ten subjects who applied a 60 mg dose of testosterone solution to each axilla. One axilla was wiped with ten alcohol towlettes. The subject then showered and washed the opposite axilla with a standard washing procedure. The second axilla was then wiped with ten alcohol towlettes. The total amount of testosterone recovered after the second wiping procedure, when compared to the amount recovered from the first wiping procedure, provides a measure of the extent of removal of testosterone by washing. Table 13 shows the testosterone recovery before and after washing for each subject.

Table 13. Testosterone Recovery, by Ten Alcohol Towlettes, from an Unwashed and a Washed Axilla

Subject	Unwashed Recovery (mg)	Washed Recovery (mg)	Effectiveness of Washing In Removing Testosterone (% removed)
1	42.8	2.1	95.1
2	43.8	4.2	90.4
3	37.0	4.2	88.7
4	45.4	2.3	95.0
5	36.8	0.9	97.5
6	47.0	2.9	93.8
7	40.8	1.2	97.1
8	41.8	10.4	75.2
9	37.7	1.0	97.3
10	48.4	2.3	95.3
Mean ± SD	42.1 ± 4.1	3.1 ± 2.8	92.5 ± 6.7

Source: NDA 22504, Module 5.3.5.4.3, Table 4, Table 6, MO Analysis

Recovery of testosterone using ten alcohol wipes is most likely an overestimation of the amount of testosterone that would be available for interpersonal transfer. Since only 3.1 mg of the applied 60 mg was recoverable using this methodology, washing the application site does reduce the potential for interpersonal transfer of testosterone.

Laboratory Findings:

There were ten subjects who reported at least one abnormal and clinically significant laboratory value in the MTE08 and MTE09 studies. These are shown in Table 14.

Table 14. Abnormal Laboratory Results Reported as Adverse Events in Studies MTE08 and MTE09

	Dose of Testosterone Solution				
	30 mg	60 mg	90 mg	120 mg	Overall
Elevated PSA (>4 ng/ml)	0	2 (1.7%)	1 (4.0%)	0	3 (1.9%)
Elevated Hematocrit (>54%)	0	6 (5.1%)	1 (4.0%)	0	7 (4.5%)
Elevated Hemaglobin (>18.1)	0	2 (1.7%)	0	0	2 (1.3%)
Elevated RBC (>6.4)	0	1 (0.9%)	0	0	1 (0.6%)
Elevated Hemoglobin A1c	0	0	0	1 (10%)	1 (0.6%)

Source: NDA 22504, Module 5.3.5.2.3, Table 12-14.

PSA Elevation

Three subjects had a PSA elevation during the study.

A 56-year-old man had a baseline PSA of 0.79 on July 14, 2008. He began study drug on July 26, 2008, and was titrated to 90 mg on October 24, 2008. His PSA at the end of Study MTE08 was 1.05 on November 28, 2008. His testosterone C_{avg} at that time was 313

ng/dL with a C_{max} of 525. He was enrolled in Study MTE09 and received his final dose of testosterone on January 21, 2009. His end-of-Study MTE09 PSA was 10.28 on January 28, 2009. This was repeated, twice, on February 2, 2009, with values of 4.36 and 3.38. The reason for the marked elevation on January 28 is not clear. The PSA had been stable for the initial 120 days of testosterone therapy. The rapid decline from approximately 10 to approximately 4 over 5 days suggests the possibility of infarction or a transient inflammatory process. There is no further follow-up information available.

A 67-year-old man had a baseline PSA of 3.9 on September 26, 2008. He began testosterone therapy on October 13, 2008, and remained on 60 mg throughout the study. His PSA at the end of MTE08 was 4.36 on February 9, 2009. It was repeated on February 19, 2009 and was 3.87. His end of MTE08 testosterone C_{avg} was 122 with a C_{max} of 133. The PSA values throughout the study are not significantly different.

A 54-year-old man had a baseline PSA of 1.27 on October 7, 2008. He began testosterone therapy on October 28, 2008, and remained on 60 mg throughout the study. His end-of-study PSA was 7.28 on February 24, 2009, and 6.36 on February 26, 2008. He was withdrawn from study MTE09 and his last dose was on February 26, 2009. He was referred for a Urology evaluation and a repeat PSA on March 11, 2009 was 3.2. A prostate biopsy showed prostate carcinoma. The underlying prostate cancer is not likely to be related to the four months of testosterone therapy. The PSA elevation may be related to the testosterone therapy.

Elevated Hematocrit:

The mean hematocrit at screening was 44%. After 120 days of testosterone therapy the mean hematocrit increased 1% with a standard deviation of 4%. After 180 days of treatment the mean hematocrit increased 3% with a standard deviation of 4%. Seven subjects had a hematocrit >54% during the course of Studies MTE08/MTE09. They are shown in Table 15.

Table 15. Subjects with Hematocrit >54%

Subject	Screening Hct	Maximal Hct	Final Hct	Screening Testosterone	Day 120 C_{AVG}	Maintenance Dose of Testosterone Solution
202-11	48	61	57	271	945	90 mg
203-21	51	57	53	26	697	60 mg
207-02	50	58	54	324	889	60 mg
210-05	48	55	53	256	256	60 mg
210-07	51	58	57	241	362	60 mg
211-26	45	61	61	280	433	60 mg
212-03	45	55	54	301	650	60 mg

Source: MO Analysis

The rise of hematocrit secondary to testosterone therapy is well known. This study excluded the enrollment of subjects with a hematocrit >51%.

Application Site Reactions:

In studies MTE08 and MTE09, the effect of this topical product on the application site was evaluated using a categorical (Draize) scale. Application site reactions and irritation do not appear to be a significant clinical issue with Axiron and can be adequately labeled.

Safety summary:

No new safety concerns with testosterone replacement therapy arose during the drug development program for Axiron. The product can be adequately dose titrated. The known adverse reactions which can occur with testosterone administration can be adequately labeled. Because of the potential for transfer to others (including children), a REMS including a Medication Guide will be required.

9. Advisory Committee Meeting

Testosterone is not a new molecular entity. Topical testosterone products were first approved in 2000 and other formulations of testosterone have been on the market for many years prior to that time. The safety issues associated with testosterone therapy are well known, and no new safety concerns were identified during the Axiron development program. No Advisory Committee meeting was convened.

10. Pediatrics

The Sponsor requested a full pediatric waiver.

A waiver was granted for the pediatric study requirement for this application because the necessary studies would be impossible or highly impractical and there are too few children with the disease/condition to study.

11. Other Relevant Regulatory Issues

Financial Disclosure:

The Sponsor has certified that the compensation of all clinical investigators was independent of the study outcome. The sponsor also certified that no investigator had a financial interest in the product or the Sponsor.

Compliance:

Compliance determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

Division of Scientific Investigations (DSI):

Three clinical sites were inspected and the data generated from these sites were found to be acceptable.

Two analytical site inspections were also performed. The DSI and Clinical Pharmacology reviewers do not believe that the deficiencies noted at these sites preclude approval of the Axiron NDA.

Division of Medication Error Prevention and Analysis (DMEPA):

DMEPA found the proprietary name Axiron to be acceptable.

DMEPA also reviewed the label and carton containers. All of the recommended changes were incorporated into the label. Acceptable carton and container labeling language was determined following discussions between DMEPA and CMC.

Office of Surveillance and Epidemiology (OSE); Division of Pharmacovigilance (DPV):

The DPV agreed with the Division that a REMS (including a Medication Guide) and labeling to include a black box warning should be required for Axiron. As previously discussed, transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a black box warning have been instituted for the two currently approved testosterone gel products.

Risk Evaluation and Mitigation Strategy (REMS):

The sponsor submitted a REMS consisting of a Medication Guide and Timetable for Assessments.

Division of Risk Management (DRISK):

DRISK reviewed the Prescribing Information and the Medication Guide and their recommendations were incorporated into both. In addition, DRISK concurred with the elements of the REMS as proposed by the Sponsor.

Division of Drug Marketing, Advertising and Communications (DDMAC):

DDMAC reviewed the proposed product labeling (PI), carton labeling, and container labeling. The DDMAC recommendations were considered during labeling negotiations with the sponsor.

Controlled Substance Staff (CSS):

The Controlled Substance Staff recommended revised labeling under Section 9 in the label ("Drug Abuse and Dependence"). The recommended changes (specifically dealing with abuse, addiction, and dependence) were incorporated into the label.

12. Labeling

- The boxed warning that has been adopted by other topical testosterone products is included in the Axiron label. This warning discusses the potential for interpersonal transfer of testosterone and the consequences of that transfer.

- The phase three study of Axiron used a dose titration design based on average testosterone concentrations over a 24 hour period. In clinical practice, titration will be done based on single blood values. The results of the Sponsor's analysis of the optimum time to draw these single values, 2 – 8 hours after application, are included in the label. The need for titration of the dose, and the method of doing so is also discussed.

- The label indicates that Axiron is contraindicated in men with breast or prostate cancer. It also includes a contraindication for women who are, or may become, pregnant.

- The label includes warnings concerning the effects of testosterone on benign prostatic hyperplasia, fertility, edema, gynecomastia, and sleep apnea.

- The potential for a significant increase in red cell mass is emphasized. The need for monitoring hemoglobin/hematocrit is included in labeling.

- The label does not include reference to secondary endpoints such as increased libido, less erectile dysfunction, etc. The phase three study was not designed to evaluate these endpoints and there was no control group to provide context to the changes seen.

Final labeling negotiations with the sponsor have been completed. SEALD has determined that the final label is acceptable.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the cross discipline team leader and primary medical officer and the clinical pharmacology, chemistry, pharmacology/toxicology, and statistical reviewers that Axiron (2% testosterone solution) should be approved for the indication "testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone."

Risk/Benefit Determination:

The Sponsor conducted one primary clinical trial (MTE08) evaluating the efficacy of Axiron testosterone 2% transdermal solution in producing serum testosterone levels within the normal range (24 hour C_{avg} levels) when the solution is used in men with low testosterone levels. This trial was adequately designed and evaluated accepted endpoints which are currently used for the evaluation of testosterone products. The pre-specified endpoints were met. Supporting evidence is submitted in several additional phase 1 and 2 studies as well as from extension trial MTE09.

In addition, the Sponsor conducted a clinical trial (MTE10) which evaluated the effect of underarm deodorant use and the effect of application site washing on product efficacy. This study, together with Study MTE08, indicates that, while deodorant use or washing the application site lowers the testosterone exposure, no adverse effect on overall efficacy was seen.

No new safety concerns with testosterone replacement therapy with Axiron arose during the drug development program for Axiron. The product can be adequately dose titrated. The known adverse reactions which can occur with testosterone administration can be adequately labeled. Because of the potential for transfer to others (including children), the label will contain a black box warning and a REMS including a Medication Guide and Timetable for Assessment will be required.

Recommendations for Risk Evaluation and Mitigation Strategies (REMS)/Post Marketing Requirement (PMR):

Transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a black box warning have been instituted for the two currently approved testosterone gel products. Because of similar potential for drug transfer with Axiron (a 2% topically applied solution), a REMS to include a Medication Guide and a Timetable for Assessments will be required of Axiron.

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

/s/

GEORGE S BENSON
11/23/2010