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APPLICATION NUMBER:
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PHARMACOLOGY REVIEW(S)

ADDENDUM

FOOD AND DRUG ADMINISTRATION

Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Date: November 19, 2010

From: Jeffrey Bray, Ph.D., Pharmacologist

To: NDA 22-504

Subject: Final Labeling

Pharm/Tox has reviewed the final submitted labeling and finds it acceptable.

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/s/

JEFFREY D BRAY
11/19/2010

LYNNDA L REID
11/19/2010
I concur with final labeling received 11/19/2010.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-504
Supporting document/s: <\\CDSESUB1\EVSPROD\NDA022504\022504.enx>
Applicant's letter date: January 25, 2010
CDER stamp date: January 25, 2010
Review Completion: September 14, 2010
Product: Axiron (testosterone solution 2 %)
Indication: Testosterone replacement in hypogonadal men
Applicant: Acrux Pharma PTY. Ltd.
Review Division: DRUP
Reviewer: Jeffrey D. Bray, Ph.D.
Supervisor: Lynnda L. Reid, Ph.D.
Division Director: Scott Monroe, M.D.
Project Manager: Jeannie Roule

Disclaimer

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1 Executive Summary

1.1 Introduction

The sponsor has submitted an application for a topical testosterone 2% solution indicated for hypogonadal men. This testosterone solution is to be applied to the axillae (armpits), potentially reducing contact-based transfer of drug product to female partners and children.

1.2 Brief Discussion of Nonclinical Findings

The sponsor submitted no new nonclinical information, and is relying on published studies of testosterone for Approval. Testosterone is the predominant male sex steroid produced by the testes and is responsible for adult male sexual characteristics. This testosterone 2% solution is to be indicated for testosterone replacement in hypogonadal men. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. However, the formulation contains an excipient not present in previously approved testosterone products. Octisalate is a penetration enhancer that is widely used in dermatological products including sunscreens and cosmetics that was found to be safe at concentrations up to 5%.

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 this testosterone 2% solution.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support Approval of testosterone 2% solution for topical (axilla) testosterone replacement in hypogonadal men.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

Class labeling is appropriate.

2 Drug Information

2.1 Drug

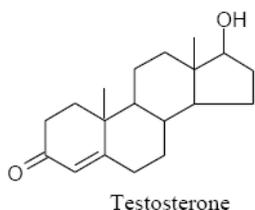
CAS Registry Number: 5949-44-0

Generic Name: testosterone

Chemical Name: (17 β)-17-hydroxyandrost-4-en-3-one

Molecular Formula/Molecular Weight: C₁₉H₂₈O₂/288.42

Structure or Biochemical Description



Pharmacologic Class: androgen

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 70,516 (Acrux Pharma, 2% testosterone solution)

NDA 21-105 (Solvay, AndroGel® 1% testosterone gel)

NDA 21-454 (Auxillium, Testim® 1% testosterone gel)

DMF (b) (4) (b) (4) testosterone)

2.3 Drug Formulation

Product is delivered via a metered pump that administers 1.5 g/actuation. The recommended starting dose is 3g (2 actuations) corresponding to 60 mg of testosterone and the dose can be titrated up to 6 g/day (120 mg testosterone).

Composition of Testosterone Solution 2% Product at Maximum Dosage of 6 g/day

Ingredient	Function	Amount		Maximal Amount in Approved Products in IID
		mg	%w/w	
Testosterone	API	120	2	--
Ethyl alcohol (b) (4)				(b) (4)
Octisalate				
Povidone				
Isopropyl alcohol				
TOTAL				

IID, Inactive Ingredient Database

2.4 Comments on Novel Excipients

Octisalate (ethylhexyl salicylate or octyl salicylate) is a penetration enhancer that is widely used in dermatological products including sunscreens and cosmetics, but not in an FDA-approved testosterone product. Dr. Lynnda Reid reviewed the use of octisalate (IND 70,516; 5/15/2007) and concluded that the Agency has found octisalate to be safe for OTC use in topical products up to concentrations of 5%. The sponsor can refer to the Agency's previous findings of safety for octisalate to support the current formulation.

2.5 Comments on Impurities/Degradants of Concern

Povidone: In the accelerated stability testing of the three registration batches (b) (4) RH) produced by Orion, a pale red color was noted. This color was not observed at 25°C for up to 15 months for registration batch, 18 months for Phase 3 batch, and 24 months for the Phase 2 batch, or at 30°C for 6 months. When the accelerated batches were tested at 12 months, the color had returned to yellow as in the original specifications. The sponsor has identified that the **povidone** (b) (4) used in the registration batches, but not the clinical trial batches, was the source of this red coloration. The main difference between the batches was that the registration batches used a batch of povidone (b) (4)

(b) (4) All attempts to isolate, enrich, and/or identify the red color forming species using state-of-the-art spectroscopic techniques failed, suggesting that it is present at levels well below the ICH Q3B(R2) quantification threshold. The sponsor states that (b) (4) will not be used in future Axiron product formulations.

Since the red color causing product is only at trace levels under accelerated conditions, and a likely source has been identified and can be eliminated through CMC specifications, the presence of the red color in the registration batches does not affect approval of this testosterone solution product.

Dimethicone Oil: The first actuation was observed to be cloudy under visual inspection. Dimethicone oil (medical grade, DMF (b) (4)) is the source of the cloudiness and it comes from the pumps. The sponsor determined that (b) (4) dimethicone oil was present in the pump, with (b) (4) found in the first actuation and the other (b) (4) in the rest of the actuations. The maximum % w/v in any actuation would be (b) (4). In a teleconference, the sponsor also stated that their investigation showed that Androgel® 1% also had dimethicone present in its first actuation.

The toxicity of dimethicone and related siloxane polymers was evaluated in the 2003 Cosmetic Ingredient Review [1]. Dimethicone is found in cosmetics as an antifoaming agent and/or an emollient skin conditioning agent. In 1998, dimethicone was present in 1,695 products reported to the FDA up to a concentration of 80%, but most in the range of 1-10%. Overall, oral dimethicone was poorly absorbed and had little toxicity reported in a number of studies in rats and dogs. A series of dermal/topical studies were conducted:

- Dimethicone (15%) had an oral LD₅₀ 16 mL/kg of in rabbits (2/5 of each sex died at 16 mL/kg).
- Dimethicone applied topically at 2008 mg/kg (unknown concentration) exposed for 24 h showed no adverse effects in 5 rats/sex after 14 days.
- Dimethicone applied topically (>90%) at 2000 mg/kg exposed for 24 h showed no adverse effects in 10 rabbits/sex after 2 weeks.
- A cat, rabbit, guinea pig, 2 rats, and 4 mice were sprayed 4 h with an atomizer containing 10 mL/kg dimethicone, and repeated 29 days later. All mice died, and mortality was not treatment related. No adverse effects were observed in other species.
- Severe irritation was noted in rabbits (n=6, sex not reported) with a Primary Irritation Index of 6.54 out of 8.0 when 0.5 mL of 100% dimethicone was applied under occlusion patches for 24 h to intact and abraded sites. Scoring was for erythema and edema.
- No irritation was observed in 4 rabbits each with intact or abraded sites after 24 h when 100% topical dimethicone was applied.
- In rabbits with 15% dimethicone applied under occlusion patches for 4h, moderate erythema (6/6) and mild edema (4/6) was observed with desquamation after 7 days and erythema persisting 10 days.
- No irritation was observed in 4 rabbits with intact or abraded sites (8 total) after 24 h when 100% dimethicone was applied.
- An unreported amount of topical dimethicone applied for 4 h produced minimal erythema and edema on 2 sites on 6 NZW rabbits after 5 h and 24 h.
- In a series of 7 studies by (b) (4) (1949, 1953, and 1954), slight "simple" irritation was produced when 35%, 50%, 99% and an unreported concentration dimethicone was applied topically as 10 applications over 14 days to ears and abdomen of rabbits (n=not reported).
- No sensitization was reported in guinea pigs >90% topical dimethicone.
- No vaginal irritation detected for up to 72h in 6 rabbits using 53% dimethicone in a mucoadhesive paste (0.5 g).
- Dermal dimethicone was not genotoxic, carcinogenic and did not cause reproductive toxicity.
- No dermal irritation in 54 men was produced when dimethicone was administered as an occluded patch for 24 h.
- No dermal sensitization was observed in 83 men (Reaction Scores all ≤1 out of 5) when 5% dimethicone was administered as an occluded patch for 24 h then rechallenged.

Dermal exposure of dimethicone in the drug product at the amounts detected appears to be reasonable safe from a pharm/tox perspective.

(b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Hypogonadal men will self-administer Axiron to the axilla region with 3 or 6 g of drug product (2 or 4 pump actuations) daily with the amount to be titrated based on achieving serum testosterone levels of 300-1000 ng/dL. One axilla will be used if 3g and both axillae will be used if 6 g.

2.7 Regulatory Background

The sponsor opened IND 70,516 to evaluate this transdermal testosterone 2% product that differs from FDA-approved testosterone transdermal products in its application site (the axilla) and formulation. Originally, nonclinical studies were requested by Dr. Krishan Raheja to evaluate the excipient octisalate since it was not listed in the Inactive Ingredient Database at the proposed concentration and Dr. Wafa Harrouk reiterated this request. However, Dr. Lynnda Reid concluded, *“The Agency has found octisalate to be safe for OTC use when used in topically applied sunscreen products at a concentration of up to 5%. The conditions of use are similar to those in the new proposed drug product and therefore, it is my opinion that the Sponsor can refer to the Agency's previous finding of safety for octisalate to support the present application.”*

The sponsor originally submitted NDA 22-504 with Form 356h selection as a 505(b)(1) application on January 25, 2010. At the time the sponsor submitted the application, FDA regulatory policy was changed such that this testosterone application would be considered to be a 505(b)(2) application. The sponsor was contacted and informed of this policy change on January 27, 2010 by e-mail. On March 3, 2010, the sponsor submitted an amended Form 356h with the 505(b)(2) box checked and no Reference List Drug listed based on Agency advice- the sponsor is relying on the literature to support the safety of testosterone. The sponsor included references to support testosterone Class Labeling for Sections 8.1 and 13.1

3 Studies Submitted

3.1 Studies Reviewed

None.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

Application #	SN# / Review#	Submission Date	Reviewer	Date
IND 70,516	Original / 1	8/11/2006	Krishan Raheja, PhD	9/22/2006
IND 70,516	0005 / 2	2/20/2007	Krishan Raheja, PhD	4/4/2007
IND 70,516	-- / 3	n/a	Lynnda Reid, PhD	5/15/2007
IND 70,516	0015 / 4	2/12/2008	Eric Andreasen, PhD	2/14/2008

4 Pharmacology

Testosterone is the primary androgen secreted by the testes and is responsible for the development, maturation, and persistence of normal male characteristics. The testosterone in this drug product is equivalent to endogenous testosterone.

Testosterone has been demonstrated to have a positive effect on male physical attributes, such as increased muscle mass, lean body weight, bone mineral density, sexual function, reduced anemia, and increased libido and feelings of well-being.

Dihydrotestosterone is the primary active metabolite and is produced by steroid 5- α -reductase located in non-genital skin, liver, and the urogenital tract of the male and in genital skin of both sexes. Both testosterone and dihydrotestosterone derive their pharmacological activities through binding to the Androgen Receptor (AR).

Drug activity related to proposed indication: Testosterone replacement therapy in hypogonadal men to alleviate symptoms of testosterone deficiency:

1. Primary hypogonadism (congenital or acquired)-testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone levels and gonadotropins (FSH, LH) above the normal range.
2. Hypogonadotropic hypogonadism (congenital or acquired)-idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum levels but have gonadotropins in the normal or low range.

6 General Toxicology

The toxicity of testosterone has been previously established in humans and nonclinical models[2]. Most changes noted occur at replacement dose levels in humans which correspond to 300-1050 ng/dL of testosterone.

Cardiovascular:

- Fluid retention/edema can occur that may contribute to congestive heart failure.
- Alteration in lipid profiles with increased cholesterol and LDL with decreased HDL levels noted that may contribute to increased risk for heart disease.
- Increases in red cells and hematocrit are often noted, and polycythemia may occur.
- Cardiovascular damage and disease has been reported.

Metabolic:

- Weight gain through muscle and fat mass changes is often noted for both genders.
- Changes in liver enzyme values occur; oral 17 α -substituted testosterone is linked to liver failure and liver cancer.
- Interactions with drugs metabolized by CYP3A4 and blood thinners have been reported.

Androgenic:

- Increased sebaceous gland activity and acne is common.
- Prostatic hypertrophy and potentially prostate cancer may occur.
- Testicular atrophy may occur, independent of fertility effects.
- Menstrual irregularities (including amenorrhea) and virilization (hair growth, acne, muscle mass increase) in human women are common

7 Genetic Toxicology

Testosterone was not mutagenic to bacteria and did not induce sperm abnormalities or micronuclei in mice treated *in vivo* (IARC supplement 6 (pp 506-507)[2] and 7 (pp 96-97)). It was reported that testosterone possesses a weak transforming effect in Syrian Hamster embryo (SHE) cells *in vitro* [3;4].

8 Carcinogenicity

The carcinogenicity potential for testosterone has been previously established. The literature references provided support the findings in the testosterone Class Labeling.

Section 13.1 (Animal data) Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rat.

The sponsor submitted nonclinical primary literature references describing the carcinogenic potential of testosterone[5-10]. A further literature search by this reviewer identifies other relevant citations by the authors of the sponsor-submitted references[11-16]. Additionally, testosterone has been demonstrated to cause mammary gland and prostate tumors in male rats and mice, but these data are superseded by human experience and are contraindicated for men that have known or suspected breast or prostate carcinoma.

9 Reproductive and Developmental Toxicology

The reproductive and developmental risk potential for testosterone has been previously established though an extensive amount of experimental evidence in the literature. The presence of testosterone during male fetal development for all mammals is required for establishment of normal male gonadal and genitalia throughout development. In contrast, prenatal exposure during fetal development can cause abnormalities to females that included virilization of the external genitalia (clitoromegaly, labial fusion, increased anogenital distances) and abnormal neurocrine or psychosexual development. Additionally, virilization of external genitalia and increased evidence of male secondary sexual characteristics (hair growth) and behaviors (aggression) have been noted human children exposed to testosterone. These effects have been documented in humans through indirect transfer of drug product, i.e. below therapeutic levels. At supraphysiologic doses given to males, reversible oligo/azospermia, and infertility can occur.

Section 8.1 Pregnancy Category X:

(b) (4)

Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

10 Special Toxicology Studies

Local tolerance, dermal irritation and transfer studies were conducted in humans.

11 Integrated Summary and Safety Evaluation

The overall toxicological profile of testosterone products is well established and both animals and humans exhibit similar toxicities. There are extensive nonclinical and clinical data with testosterone products including transdermal applications. The excipient octisalate is considered reasonably safe at 5% based on low toxicity and OTC usage in topical sunscreens. Dimethicone oil is present in the first few pump actuations but is not a safety concern due to its small amount, presence in clinical batches, low dermal toxicity and ubiquitous presence in many cosmetics and foods. A red coloration observed in accelerated stability registration batches was investigated by the sponsor. It was determined to be present at trace amounts and only in the accelerated stability batches due to a certain batch of (b) (4) povidone, (b) (4). Based on these facts, a human safety risk is considered low. Nonclinical data support approval of topical testosterone solution 2%.

12 Appendix/Attachments

Reference List

1. Nair B. Final report on the safety assessment of stearoxy dimethicone, dimethicone, methicone, amino bispropyl dimethicone, aminopropyl dimethicone, amodimethicone, amodimethicone hydroxystearate, behenoxy dimethicone, C24-28 alkyl methicone, C30-45 alkyl methicone, C30-45 alkyl dimethicone, cetearyl methicone, cetyl dimethicone, dimethoxysilyl ethylenediaminopropyl dimethicone, hexyl methicone, hydroxypropyldimethicone, stearamidopropyl dimethicone, stearyl dimethicone, stearyl methicone, and vinyl dimethicone. Int J Toxicol 2003; 22 Suppl 2:11-35.
2. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex hormones (II). IARC Monogr Eval Carcinog Risk Chem Hum 1979; 21:11-561.
3. Lasne C, Lu YP, Orfila L, Ventura L, Chouroulinkov I. Study of various transforming effects of the anabolic agents trenbolone and testosterone on Syrian hamster embryo cells. Carcinogenesis 1990; 11:541-7.

4. Tsutsui T, Komine A, Huff J, Barrett JC. Effects of testosterone, testosterone propionate, 17 beta-trenbolone and progesterone on cell transformation and mutagenesis in Syrian hamster embryo cells. *Carcinogenesis* 1995; 16:1329-33.
5. Reuber MD. Effect of age and testosterone on the induction of hyperplastic nodules, carcinomas, and cirrhosis of the liver in rats ingesting n-2-fluorenyldiacetamide. *Eur J Cancer* 1976; 12:137-41.
6. Reuber MD. Influence of sex and sex hormones on transplantable hepatocellular carcinoma in the rat. *Pathol Microbiol (Basel)* 1975; 42:59-65.
7. Schenken JR, Burns EL. Spontaneous Primary Hepatomas in Mice of Strain C3H III. The Effect of Estrogens and Testosterone Propionate on Their Incidence. *Cancer Res* 1943; 3:693-6.
8. van Nie R, SMIT GM, MUHLBOCK O. The induction of uterine tumours in mice treated with testosterone. *Acta Unio Int Contra Cancrum* 1962; 18:194-6.
9. van Nie R. Biological aspects of the genesis of uterine tumours induced in mice by testosterone. *Jaarb Kankeronderz Kankerbestrijd Ned* 1964; 14:247-52.
10. Kemp CJ, Leary CN, Drinkwater NR. Promotion of murine hepatocarcinogenesis by testosterone is androgen receptor-dependent but not cell autonomous. *Proc Natl Acad Sci U S A* 1989; 86:7505-9.
11. Kemp CJ, Drinkwater NR. Genetic variation in liver tumor susceptibility, plasma testosterone levels, and androgen receptor binding in six inbred strains of mice. *Cancer Res* 1989; 49:5044-7.
12. FIRMINER HI, Reuber MD. Influence of adrenocortical, androgenic, and anabolic hormones on the development of carcinoma and cirrhosis of the liver in A x C rats fed N-2-fluorenyldiacetamide. *J Natl Cancer Inst* 1961; 27:559-95.
13. Reuber MD. Influence of hormones on N-2-fluorenyldiacetamide-induced hyperplastic hepatic nodules in rats. *J Natl Cancer Inst* 1969; 43:445-52.
14. Reuber MD. Importance of thyroid hormone and testosterone in the induction of carcinoma and cirrhosis of the liver in female Wistar rats ingesting N-2-fluorenyldiacetamide. *J Natl Cancer Inst* 1966; 36:775-81.
15. Reuber MD. ROLE OF THE ADRENAL GLANDS IN THE DEVELOPMENT OF LESIONS OF THE LIVER IN RATS INGESTING N-2-FLUORENYLDIACETAMIDE. *J Natl Cancer Inst* 1965; 34:587-94.
16. BENEDETTI EL, van Nie R. On the histology and the fine structure of uterine tumours induced by testosterone in mice. *Acta Unio Int Contra Cancrum* 1962; 18:197-9.

17. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Sex hormones (II). IARC Monogr Eval Carcinog Risk Chem Hum 1987; 21:96-99.

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/s/

JEFFREY D BRAY
09/22/2010

LYNNDA L REID
09/22/2010

I concur with Dr. Bray's assessment. PT data support approval.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-504 **Applicant: Acrux Pharma** **Stamp Date: January 25, 2010**
PTY. Ltd.

Drug Name: Axiron **NDA Type: 505(b)2**
(testosterone solution) 2 %

45-Day Filing Review Date: **March 11, 2010**
74-Day Letter Date: **April 9, 2010**
Expected Date of Draft Review: **June 1, 2010**
PDUFA Goal date: **November 25, 2010**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	NA		No P/T section was submitted to the original NDA. Sponsor was contacted and provided primary literature on testosterone carcinogenicity and two IARC reviews of the toxicology of testosterone.
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	NA		See Comment 1.
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	NA		See Comment 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?		X	No nonclinical studies were requested or performed to support the NDA. The sponsor does not identify a RLD. The sponsor submitted 8 nonclinical references.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	NA		
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?	NA		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	NA		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	NA		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Format and class labeling appear to be reasonable for this testosterone product.
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	X		The sponsor used Octisalate USP as a penetration enhancer at a concentration not previously qualified. A review of octisalate suggested that it was reasonably safe from a pharm/tox perspective at the proposed concentration. The sponsor refers to DMF (b) (4) [REDACTED] (b) (4)
11	Has the sponsor addressed any abuse potential issues in the submission?	NA		
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	NA		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments: None.

Jeffrey Bray, Ph.D. 2/26/2010

 Reviewing Pharmacologist Date

Lynnda Reid, Ph.D. 3/8/2010

 Team Leader/Supervisor Date

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

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