CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022504Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Reproductive and Urologic Products

NDA/BLA #s: NDA 022504
Product: Axiron® (testosterone) topical solution
APPLICANT: Acrux Pharma Pty Ltd.
FROM: George Benson, M.D.
DATE: November 18, 2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Axiron® (testosterone) topical solution to ensure that the benefits of the drug outweigh the risk of secondary exposure of children to testosterone due to drug transfer from adult men using this product. In reaching this determination we considered the following:

A. It has been estimated that 4 to 5 million American men have hypogonadism of whom 5 percent receive testosterone therapy. While it is not possible to estimate the size of the population likely to use topical testosterone products, of which Axiron® (testosterone) topical solution is a member of the class, these products have the largest market share among testosterone-containing products. In 2007 alone, approximately 2.5 million prescriptions were dispensed for all formulations of testosterone containing products.

B. Hypogonadism in men is a serious disease resulting from a lack of endogenous testosterone. The aim of testosterone therapy in men with hypogonadism is to restore or normalize male secondary sexual characteristics (such as beard, body hair, voice) and male sexual behavior, and to promote normal male somatic development (muscle mass, bone). The consequences of long term testosterone deficiency in hypogonadal men may include decreased muscle mass

and strength, decreased sexual function and osteoporosis.

C. Based on the phase 3 trial, Axiron® (testosterone) topical solution was demonstrated to be effective in producing serum total testosterone concentrations within the normal range in the majority of hypogonadal men studied.

D. Axiron® (testosterone) topical solution will be used for replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Treatment is expected to continue throughout the patient's lifetime.

E. Postmarketing reports of secondary exposure of children to testosterone gel products have appeared. These reports prompted the Agency to include a Boxed Warning in all testosterone gel product labeling and a REMS (including a Medication Guide) was required of all of these products. Axiron® (testosterone) topical solution is also a topically applied testosterone product which has the potential for transfer to others (including women and children). Topically applied testosterone products have also been associated with other adverse effects, including gynecomastia, edema, and sleep apnea. Additionally, exogenous administration of testosterone may lead to azoospermia.

F. Axiron® (testosterone) topical solution is not a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Axiron® (testosterone) topical solution. FDA has determined that Axiron® (testosterone) topical solution poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Axiron® (testosterone) topical solution. FDA has determined that Axiron® (testosterone) topical solution is a product for which patient labeling could help prevent serious adverse effects and has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Axiron® (testosterone) topical solution and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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

/s/

JEANNIE M ROULE
11/17/2010

GEORGE S BENSON
11/18/2010

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 19, 2010
To:	Scott Monroe, MD, Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	Claudia Karwoski, PharmD, Director **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	AXIRON (testosterone) Solution for Topical Use
Application Type/Number:	NDA 22-504
Applicant/sponsor:	Acrux Pharma Pty Ltd.
OSE RCM #:	2010-1107

1. INTRODUCTION

This memorandum is in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document for AXIRON (testosterone) Solution for topical use.

The DRISK review of the Medication Guide will be provided under a separate cover. The DRISK review of the methodology and survey instruments to be submitted by the Applicant to evaluate the REMS will be provided under separate cover.

2. BACKGROUND

In May of 2009, the FDA announced that it was requiring the sponsors of two existing FDA approved transdermal testosterone products to include new safety information in the labeling for their testosterone products. The FDA also notified the sponsors that they were required to submit a proposed REMS and Medication Guide for these products. The new safety information referred to by the FDA were cases of secondary exposure of children to testosterone due to drug transfer from adult males using testosterone gel products, presumably resulting from the failure to follow appropriate instructions for use. The particular populations at risk of inadvertent transfer are children and adult females. The revised labels, FDA approved REMS and Medication Guides of the two marketed transdermal testosterone gel products were published in September of 2009.

Acrux Pharma Pty Ltd. voluntarily submitted a proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 22-504 AXIRON™ (testosterone) Solution for topical use, as it believes the additional information for patients will assist in reducing the risk of inadvertent secondary exposure of testosterone to children. In particular, the sponsor believes the inclusion of a Medication Guide with the product will promote the correct adherence by patients to the directions for the use of AXIRON, and inform the patient about known potential side effects with the product.

3. MATERIAL REVIEWED

- Proposed AXIRON (testosterone) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document submitted on May 12, 2010 and received by DRISK on June 04, 2010.

4. RESULTS OF REVIEW

In our review of the proposed REMS we have:

- Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

5. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

Please note, the timetable for submission of the assessment is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments do not need to be reviewed or approved prior to approval of the REMS

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to Acrux Pharma Pty Ltd.:

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

a. **GOAL**

Revise you goal as follows:

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

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

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

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

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

d. Regarding your REMS Assessment Plan

1. The submitted methodology lacks sufficient detail to complete a review. We will defer comment of your proposed assessment until you have submitted a full protocol and survey instrument.
2. Submit for review the detailed plan you propose to use to evaluate patients' understanding about the safe use of Axiron. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." If the plan is to conduct the required assessment using a survey, make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Axiron.
3. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

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

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

   Explain how you select recruitment sites.

   Submit for review any recruitment advertisements.
4. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of patient knowledge for each key risk(s).
5. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
6. Ensure the sample is demographically representative of the population who use the drug (patients).
7. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
8. List the inclusion criteria. For example, eligible patient respondents must be:

   - Age 18 or older
   - Currently taking Axiron or have taken the drug in the past 3 months
   - Not currently participating in a clinical trial involving Axiron
   - Not a healthcare provider

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

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

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

   Explain how you train surveyors.

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

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

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

12. Clarify in your methodology that respondents are eligible for one wave of the survey only.

13. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

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

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

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

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

    Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all

that apply." Ensure that each question has an "I don't know" answer option.

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

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

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

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

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

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

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

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

    - Who gave you the Medication Guide for Axiron? (Select all that apply)
        a) My doctor or someone in my doctor's office
        b) My pharmacist or someone at the pharmacy
        c) Someone else - please explain:
           _____
        d) I did not get a Medication Guide for Axiron
    - Did you read the Medication Guide?
        a) All,
        b) Most,
        c) Some,

d) None

- Did you understand what you read in the Medication Guide?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did someone offer to explain to you the information in the Medication Guide?
    a) Yes, my doctor or someone in my doctor's office
    b) Yes, my pharmacist or someone at the pharmacy
    c) Yes, someone else – please explain:
    _____
    d) No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
    a) All,
    b) Most,
    c) Some,
    d) None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

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

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

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

/s/

SHAWNA L HUTCHINS
10/19/2010

CLAUDIA B KARWOSKI
10/19/2010
concur