

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

**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: 203098
Product: testosterone gel
APPLICANT: Perrigo Israel Pharmaceuticals, Ltd
FROM: Audrey Gassman, MD
DATE: February 1, 2013

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 testosterone gel to ensure that the benefits of the drug outweigh the risks of secondary exposure due to drug transfer from adult males using testosterone gel products to children. 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 testosterone gel products, of which testosterone gel is a member of the class, these products have the largest market share among testosterone-containing products. In 2007 alone, approximately (b) (4) 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, testosterone gel was demonstrated to be effective in producing serum total testosterone concentrations within the normal range in the majority of hypogonadal men studied.
- D. Testosterone gel 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. In addition, to postmarketing reports of secondary exposure of children to testosterone, testosterone gel products, of which testosterone gel is a member of the class, have been associated with various other adverse effects, including gynecomastia, edema, and sleep apnea. Additionally, exogenous administration of testosterone may lead to azoospermia.
- F. Testosterone gel is not a new molecular entity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that testosterone gel 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 testosterone gel. FDA has determined that testosterone gel is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk of which patients should be made aware because information concerning the risk could affect patients' decisions to use or continue to use testosterone gel. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed testosterone gel.

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

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/s/

MEREDITH ALPERT
01/31/2013

SURESH KAUL
01/31/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

**Addendum to the February 29, 2012
Final Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: November 20, 2012

Reviewer: Cynthia LaCivita, Pharm.D.
Risk Management Analyst, Team Leader
Division of Risk Management

Division Director: Claudia Kawasaki, Pharm.D.
Director, Division of Risk Management

Drug Name(s): Testosterone gel C III
Therapeutic Class: Androgen
Dosage and Route: Topical
Application Type/Number: NDA 203098
Submission Number: Original-1
Applicant/sponsor: Perrigo Israel Pharmaceuticals, Ltd.
OSE RCM #: 2011-2508

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This review provides Division of Risk Management (DRISK) recommendations on the proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 203098 submitted on December 12, 2011. The proposed REMS includes a Medication Guide (MG) and a timetable for submission of assessments. The subject of this review is the REMS document. The MG will be reviewed by the Division of Medical Policy Programs (DMPP) under separate cover.

2 MATERIALS REVIEWED

- December 12, 2011(sequence 0012) Proposed REMS, REMS supporting document and MG
- November 14, 2012, Revised REMS submitted by e-mail to J. Roule
- Approved REMS for Testosterone topical products (NDAs 21015, 22309, 22504, 21463)
- DRISK REMS Review by C.LaCivita, Dated February 29, 2012

3 PROPOSED TESTOSTERONE GEL C-III REMS

On November 14, 2012, the sponsor submitted a revised REMS document via email.

The applicant agreed to officially resubmit a final REMS document reflecting all DRISK/DRUP revisions.

4 DISCUSSION

DRISK compared the proposed REMS document for Testosterone Gel to the approved REMS' documents for approved testosterone topical products. It is consistent with the other approved REMS.

Reference to the percentage of testosterone was removed from the REMS document to accurately reflect dosing and administration in the product labeling. Product labeling does not include percentages, dosing units are in milligrams.

5. RECOMMENDATIONS

DRISK finds the revised REMS document to be acceptable. (See attachment) The month and year of initial approval should be included when DRUP takes action on this submission.

The MG review by Division of Medical Policy Programs (DMPP) will be provided under separate cover.

Initial REMS Approval: XX/2012

NDA 203098 Testosterone Gel, CIII

Drug Class and Formulation: Testosterone Gel Products

Perrigo Israel Pharmaceutical Ltd.

Industrial Zone

Yeruham, Israel 80500

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(s):

To inform patients about the serious risks associated with the use of testosterone gel.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each testosterone gel, prescription in accordance with 21 CFR § 208.24.

The Medication Guide is appended.

B. Timetable for Submission of Assessments

Perrigo Israel Pharmaceuticals Ltd. will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Perrigo Israel Pharmaceuticals Ltd. will submit each assessment so that it will be received by FDA on or before the due date.

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/s/

MARY J DEMPSEY

11/20/2012

Entered into DARRTS for Cynthia LaCivita

CLAUDIA B MANZO

11/20/2012

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date: February 29, 2012

Reviewer: Cynthia LaCivita, Pharm.D.
Risk Management Analyst, Team Leader
Division of Risk Management

Division Director: Claudia Kawasaki, Pharm.D.
Director, Division of Risk Management

Drug Name(s): Testosterone gel (b) (4) C III

Therapeutic Class: Androgen

Dosage and Route: Topical

Application Type/Number: NDA 203098

Submission Number: Original-1

Applicant/sponsor: Perrigo Israel Pharmaceuticals, Ltd.

OSE RCM #: 2011-2508

TSI #: 585

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1 INTRODUCTION

This review provides Division of Risk Management (DRISK) recommendations on the proposed Risk Evaluation and Mitigation Strategy (REMS) for NDA 203098 submitted on December 12, 2011. The proposed REMS is comprised of a Medication Guide (MG) and a timetable for submission of assessments. The subject of this review is the REMS document. The MG will be reviewed by the Division of Medical Policy Programs (DMPP) under separate cover.

1.1 BACKGROUND AND REGULATORY HISTORY

On July 5, 2011 the Agency received an application from Perrigo Israel Pharmaceuticals, Ltd., for Testosterone Gel (b) (4) C – III, New Drug Application (NDA) 203098 with the proposed indication of replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

In 2009, the Agency determined that a REMS with a MG and Timetable for Submission of Assessments was necessary to ensure the benefits of testosterone topical gels outweigh the risk of secondary exposure of children to testosterone which may cause virilization. The first REMS for these products was approved September 18, 2009.

If approved, this NDA will be the fifth topical gel product containing testosterone to be marketed.

2 MATERIALS REVIEWED

- December 12, 2011(sequence 0012) Proposed REMS
- Approved REMS for Testosterone topical products (NDAs 21015, 22309, 22504, 21463)

3 PROPOSED TESTOSTERONE GEL (b) (4) C-III REMS

The sponsor submitted a REMS document, REMS supporting document and a MG.

4 DISCUSSION

DRISK compared the proposed REMS document for Testosterone Gel (b) (4) to the approved REMS' documents for approved testosterone topical products. It will be consistent with the other approved REMS with the necessary revisions that we provided.

5. RECOMMENDATIONS

DRISK finds the REMS document to be acceptable providing the sponsor makes the necessary changes identified in the track changes version of the REMS document (see attached).

The MG review by Division of Medical Policy Programs (DMPP) will be provided under separate cover.

Initial REMS Approval: ~~XX~~^{(b) (4)}/2012

NDA 203098 Testosterone Gel, 1%-CIII

Drug Class and Formulation: Testosterone Gel Products

Perrigo Israel Pharmaceutical Ltd.

Industrial Zone

Yeruham, Israel 80500

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(s):

T. ^{(b) (4)} to inform patients about the serious risks associated with the use of Testosterone Gel, 1%.

II. REMS ELEMENTS:

A. ~~Medication Guide~~

~~Medication~~^{(b) (4)} Medication Guide will be dispensed with each Testosterone Gel, 1% prescription in accordance with 21 CFR § 208.24.

The ^{(b) (4)} Medication Guide is appended ^{(b) (4)}.

B. Timetable for Submission of Assessments

Perrigo Israel Pharmaceuticals Ltd. will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Perrigo Israel Pharmaceuticals Ltd. will submit each assessment so that it will be received by FDA on or before the due date.

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/s/

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03/02/2012

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