



NDA 022504/S-012

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Marija Popovic, PhD
Consultant Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Popovic:

Please refer to your Supplemental New Drug Application (sNDA) dated and received March 11, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Axiron® (testosterone) topical solution.

We acknowledge receipt of your amendment dated, April 10, 2015.

We also refer to our letter dated, February 9, 2015, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for all approved testosterone replacement therapies. This information pertains to the appropriate indicated population for testosterone replacement therapy and the potential risk of major adverse cardiovascular events associated with testosterone replacement therapy.

This supplemental new drug application provides for revisions to the labeling for testosterone gel, consistent with our February 9, 2015, letter and electronic communication dated March 27, 2015. Labeling revisions to the prescribing information are as follows:

- Indications and Usage: addition of a Limitation of Use statement concerning “age-related” hypogonadism and removal of “idiopathic” from hypogonadotropic hypogonadism
- Dosage and Administration: addition of a recommendation to measure and ensure that serum testosterone concentrations are below the normal range to confirm the diagnosis of hypogonadism prior to initiating testosterone replacement therapy
- Warnings and Precautions: addition of a new Warning regarding the possible increased risk of major adverse cardiovascular events
- Revisions to the Adverse Reactions/Postmarketing Experience and Clinical Pharmacology sections

The Medication Guide was also revised to reflect these changes accordingly.

This supplement new drug application also provides for a proposed modification to the approved risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Axiron was originally approved on November 23, 2010, and REMS modifications were approved on March 31, 2011, and last modified on June 19, 2014. The REMS consists of a Medication Guide, and a timetable for submission of assessments of the REMS. In order to ensure the benefits of Axiron outweigh its risks, we determined that you were required to make the following REMS modification: to revise the Medication Guide to include the risk of major adverse cardiovascular events associated with testosterone replacement

therapy and to add information regarding the natural rubber latex content of the bottle and applicator cup that is consistent with the FDA Final Guidance: Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex.

Your proposed modified REMS, submitted on March 11, 2015, and appended to this letter, is approved.

The modified REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS will remain the same as that approved on November 23, 2010.

There are no changes to the REMS assessment plan described in our November 23, 2010, letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the

proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 022504 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 022504 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022504
CHANGES BEING EFFECTED IN 30 DAYS
< other supplement identification >
PROPOSED MINOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 022504
PRIOR APPROVAL SUPPLEMENT
< other supplement identification >
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 022504
PRIOR APPROVAL SUPPLEMENT**

**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022504
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 022504

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:

Content of Labeling
REMS

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

/s/

CHRISTINE P NGUYEN
05/11/2015