

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

OTHER ACTION LETTER(s)



NDA 203098

COMPLETE RESPONSE

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received, July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone gel.

We acknowledge receipt of your amendments received July 28, August 4, 8, 11, and 25, September 14, November 8, 21 (2), and 22, December 1, and 12, 2011; January 19, February 1, 6, 21, and 29, March 5, 7, 22, and 26, and April 13, 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

Your Bioequivalence (BE) study between the proposed product (testosterone gel) and the reference listed drug (RLD; AndroGel® 1%) cannot be adequately evaluated. As outlined in Form 483s (dated March 1 and 30, 2012), there are unresolved clinical and bioanalytical site inspection deficiencies. Specifically, a major deficiency of missing dosing records for study period 3 was reported in FDA Form 483. As a result, data from study period 3 were excluded from statistical evaluation. The resultant small sample size makes it unfeasible to do any meaningful statistical analysis for the BE evaluation.

In addition, as reported in Form 483 from the bioanalytical site inspection, the measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and quality control samples. To date, you have not adequately addressed these deficiencies.

Information Needed to Address the Clinical Pharmacology Deficiency

A study demonstrating the safety and efficacy of the proposed product (testosterone gel) needs to be conducted. This can be done by conducting a pivotal BE study using an approved testosterone

product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA re-submission. We recommend that you submit the study protocol to the Agency before initiation of the study.

Alternatively, you may provide an adequate response to the outstanding deficiencies listed in Form 483s. If you choose to submit a response to these deficiencies, you should also submit a letter to your NDA notifying the Division that you have done so.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge the submission of your proposed REMS on December 12, 2011, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jeannie Roule, Regulatory Project Manager, at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting, Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
05/03/2012