

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22309Orig1s000**

**OTHER ACTION LETTER(s)**



NDA 022309

**COMPLETE RESPONSE**

Unimed Pharmaceuticals, LLC  
Attention: Kathryn Penhale-Unz  
Director, Regulatory Affairs  
901 Sawyer Road  
Marietta, GA 30062

Dear Ms. Penhale-Unz:

Please refer to your new drug application (NDA) dated February 11, 2009, received February 12, 2009, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AndroGel<sup>®</sup> (testosterone gel) 1.62%.

We acknowledge receipt of your submissions dated February 11, March 4 and 10, May 14, June 11, July 14, September 3(2), and 18, November 9, December 1(2), 4, 8, 15, and 24, 2009, and January 15 and 21, and February 2, 2010.

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

### **CLINICAL and CLINICAL PHARMACOLOGY DEFICIENCY**

Based upon results from the Phase 1 transfer Study S176.1.009, you proposed to change the method of application for doses of AndroGel 1.62% of 3.75 gm and 5 gm. You now recommend that 5 gm be applied equally to 4 different anatomic sites, including both arms/shoulders and both sides of abdomen. Similarly, you now recommend that a 3.75 gm dose be applied equally to 3 anatomic sites. This new application method differs from the application method used in the Phase 3 Study S176.3.104, in which these same doses were applied to either the shoulders/upper arms or the abdomen, but not to both at the same time. The information that you provided to support comparability of testosterone concentrations associated with the new application method and those associated with the Phase 3 method is considered inadequate for the following reasons:

- The information comes from a subgroup of Phase 3 study patients who deviated from the protocol by applying AndroGel 1.62% in a manner contrary to the protocol instructions.
- The topical application of AndroGel 1.62% on the pharmacokinetic (PK) days in these patients was not properly supervised.
- This subgroup was small, consisting of only 41 patients, with a total of only 66 potentially relevant application events.

- Of the 41 patients in this subgroup, 17 applied the gel in a manner other than your current proposal (e.g. applying 5 gm to 3 anatomic sites and 3.75 gm to 4 anatomic sites).
- In the remaining patients in this subgroup:
  - Use of the new method was sporadic, with a small amount of PK data collected. A total of 17 patients provided just 1 PK profile, 4 patients provided 2 PK profiles, and 2 patients provided 3 PK profiles.
  - The case report form listings are insufficient to determine whether AndroGel 1.62% was applied evenly to the anatomic sites.
  - Information is not available to determine whether the method of application was consistent throughout the study.

In addition, application site skin irritation assessments have not been conducted following continuous once daily application to four anatomic sites.

We conclude, therefore, that the testosterone PK of the new application method relative to the Phase 3 method is currently unknown.

### **Information Needed To Address the Clinical and Clinical Pharmacology Deficiency**

Conduct and provide a complete report for a steady-state, 2-way crossover, comparative bioavailability study of AndroGel 1.62% in hypogonadal males, evaluating the following two regimens:

1. Application of a 5 gm dose to 2 anatomic sites utilizing the upper arms/shoulders or abdomen on a rotating basis, as per the instructions for use in the Phase 3 Study S176.3.104, versus
2. Application of a 5 gm dose to 4 anatomic sites utilizing both upper arms/shoulders and both sides of the abdomen, as per the instructions for use in Study S176.1.009.

In addition to assessing serum testosterone concentrations, this study should capture data for application site skin irritation.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

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)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for AndroGel (testosterone gel) 1.62%, if it is approved, 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. The REMS, once approved, will create enforceable obligations.

We acknowledge receipt of your proposed REMS, included in your submission dated

September 2, 2009. We will continue discussion of your proposed REMS after your complete response to the action letter has been submitted.

### **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>.

### **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 one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. 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 Health Project Manager, at (301) 796-3993.

Sincerely,

*{See appended electronic signature page}*

George Benson, M.D.  
Deputy Director  
Division of Reproductive and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22309

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ORIG-1

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UNIMED  
PHARMACEUTICA  
LS INC

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ANDROGEL

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEORGE S BENSON

03/12/2010