

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-350**

**APPROVABLE LETTER 1**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

NDA 21-350

Skye Pharma Inc.  
Attention: Gordon L. Schooley, Ph.D.  
Chief Scientific Officer  
10450 Science Center Drive  
San Diego, CA 92121

Dear Dr. Schooley:

Please refer to your new drug application (NDA) dated June 22, 2001, received June 25, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Triglide (fenofibrate tablets), 50mg and 160 mg.

We acknowledge receipt of your submissions dated February 24, 2003, and March 31, May 19, July 30 (2), October 15 and 26, and November 16, 2004.

The March 31, 2004, submission constituted a complete response to our April 24, 2002, action letter.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, the following deficiencies will have to be addressed:

Biopharmaceutics:

1. With limited dissolution data provided, it appeared that the 160 mg tablets dissolved similarly in 0.025 M SLS [REDACTED] media. Therefore, the dissolution method using the lower SLS concentration of 0.025 M is recommended. Since the dissolution data of 50 mg tablets using 0.025 M SLS was lacking, provide data for three batches [REDACTED] (batch) of the 50 mg strength under the condition of USP Apparatus 2 at 50 rpm in 0.025 M SLS medium. The biowaiver for the 50 mg tablets will be determined based on the similarity between the dissolution profiles of the 50 mg and 160 mg tablets using USP Apparatus 2 at 50 rpm in 0.025 M SLS medium.

Chemistry, Manufacturing, and Controls (CMC):

2. The application lacks sufficient evidence that the drug product (Lipanthyl 200M) used in the bioequivalence (BE) study (FEN101-C1-001) is the same drug product from the CMC perspective as the reference drug, Tricor (fenofibrate, micronized) Capsules, 200 mg (Abbott's NDA 19-304). Please provide information on the equivalence between the two products. We reference the letter dated April 12, 2002, addressed "To whom it may concern" under Fournier

Laboratories letterhead. Please provide the basis on which these representations are made. Additionally, provide evidence that the Lipanthyl 200M and Tricor 200 mg capsule products are identical in qualitative and quantitative composition with regard to both active and inactive ingredients. Also provide evidence that the manufacturing processes and controls are the same for both products. Useful evidence to help support your assertions might be, for example: Evidence that the drug substance used for both products meets the same specifications, comparative batch records, comparative detailed manufacturing descriptions, and comparisons of process controls. In addition, provide certificates of analysis for Lipanthyl 200M and Tricor 200 mg capsules using the U.S. NDA approved procedures for Tricor 200 mg capsules, as well as evidence of authorization to access the Tricor 200 mg NDA specifications (NDA 19-304).

3. The drug product specification for appearance is not acceptable. We recommend that you either (1) justify that the discoloration is not a safety concern [i.e., provide a cause of the yellow color (e.g., identify and quantify the compound causing the yellow color) and provide a safety evaluation] or (2) change the acceptance criteria for appearance so that discoloration would be unacceptable. If discoloration up to a certain level is proven to be safe, and if you want to allow a certain level of discoloration, then you should develop a quantitative method to measure the amount of discoloration and a quantitative acceptance criterion should be set. In that case, the quantitative method and the quantitative acceptance criterion should be part of the drug product release and stability specifications. The terms "slight coloration" and "noticeable coloration" used in the current method to evaluate appearance are too subjective and should be replaced by quantitative measurements.
4. Lower the drug product moisture content acceptance criterion below \_\_\_\_\_, w/w. Tablet moisture levels at or above \_\_\_\_\_ w/w may cause the tablets to become sticky and result in damage to the tablets when removed from the blister cavity.
5. Provide an updated listing of drug substance specifications and drug product specifications for release and stability.

Regulatory:

6. Since the submission of the original application, an application for 160 mg fenofibrate tablets, Tricor Tablets (NDA 21-203), was approved. The Tricor Tablet product is the pharmaceutical equivalent to Triglide and therefore raises issues regarding changes in listed drugs and appropriate patent certifications that need to be resolved before approval. If you change your listed drug(s) to NDA 21-203 or to NDA 19-304 and NDA 21-203, you need to do the following:
  - (a) Submit a new application as required under the Medicare Modernization Act when there is a change in the listed drug. (All information in this application [NDA 21-350] may be incorporated by reference to the new NDA, and a User Fee will not be required for the new application.)
  - (b) Cite NDA 21-203 as an additional listed drug referenced by your 505(b)(2) NDA.
  - (c) Provide patent certifications for NDA 21-203.
7. Provide financial disclosure information and the required forms for the pharmacokinetic study submitted July 30, 2004.

Labeling:

8. Revise your draft package insert as indicated in the enclosed labeling. Changes to your March 31, 2004, labeling are shown with underlining for additions and strikethroughs for deletions. Also, please note the comments in the right margin concerning certain options. We remind you also to submit the "content of labeling" in electronic format as described in 21 CFR 314.50(l)(5) and in the format described at the following website:  
<http://www.fda.gov/oc/data>.
9. Submit color mock-ups of your container and carton labels with the proprietary name Triglide.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend this/ application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug  
Products, HFD-510  
Office for Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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David Orloff  
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