



NDA 22363/S-010

**SUPPLEMENT APPROVAL**

Kowa Pharmaceuticals America, Inc.  
US Agent for Kowa Company Limited  
Attention: John M. Ostrander, Ph.D.  
Senior Director, Regulatory Affairs  
530 Industrial Park Blvd  
Montgomery, AL 36117

Dear Dr. Ostrander:

Please refer to your Supplemental New Drug Application (sNDA) dated September 20, 2012, received September 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LIVALO (pitavastatin) Tablets, 1 mg, 2 mg, and 4 mg.

We acknowledge receipt of your amendments dated October 22 and 26, 2012. We also acknowledge receipt of your email dated October 31, 2012, that includes the agreed-upon labeling.

We also refer to our letter dated August 22, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for HMG-CoA reductase inhibitor (statin) drugs. This information pertains to the risk of immune-mediated necrotizing myopathy (IMNM).

Supplemental new drug application, S-010, provides for revisions to the labeling for Livalo. The agreed upon changes to the language included in our August 22, 2012, letter are as follows (additions are noted by underline and deletions are noted by ~~strike through~~).

In the Full Prescribing Information, under **WARNINGS AND PRECAUTIONS, 5.1 Skeletal Muscle Effects:**

There have been rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, associated with (b) (4) statin (b) (4) use. (b) (4) IMNM (b) (4) is characterized by: proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment; muscle biopsy showing necrotizing myopathy without significant inflammation; improvement with immunosuppressive agents.

(b) (4)

In the Full Prescribing Information, under **ADVERSE REACTIONS, 6.2 Postmarketing Experience**, add:

Adverse reactions associated with LIVALO therapy reported since market introduction, regardless of causality assessment, include the following: abdominal discomfort, abdominal pain, dyspepsia, nausea, asthenia, fatigue, malaise, hepatitis, jaundice, fatal and non-fatal hepatic failure, dizziness, hypoesthesia, insomnia, depression, interstitial lung disease, erectile dysfunction, ~~and~~ muscle spasms, [REDACTED]

There have been rare reports of immune-mediated necrotizing myopathy [see *Warnings and Precautions (5.1)*]

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 patient package insert), 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 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).

## **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/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. 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 Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

*{See appended electronic signature page}*

Amy G. Egan, M.D., M.P.H.  
Deputy Director for Safety  
Division of Metabolism and Endocrinology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

ENCLOSURE:  
Content of Labeling

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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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AMY G EGAN  
10/31/2012