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RESEARCH**

APPLICATION NUMBER:

22-363

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022363

NDA APPROVAL

Kowa Research Institute, Inc.
Agent for Kowa Company, Limited
Attention: Ross Laderman
Senior Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Please refer to the new drug application (NDA) you submitted on behalf of Kowa Company, Limited, dated October 1, 2008, received October 3, 2008, 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 submissions dated November 21 and 26 (2 submissions), and December 12, 2008, and January 5, 14, 20 (2 submissions), 23, 26, and 29, February 6 (2 submissions), 16 and 20 (2 submissions), March 5 (2 submissions), 9 (2 submissions), 10, and 11 (3 submissions), April 1, 14, 16, 23, 29, and 30, May 5, 6, and 29, June 8, (2 submissions), 9 and 22, and July 6, 7, 9, 13, and 27 (2 submissions), 2009.

This new drug application provides for the use of Livalo (pitavastatin) Tablets for patients with primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein (Apo) B, and triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C).

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

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, that is identical to the enclosed labeling (text for the package insert). Upon receipt, we will transmit that version to the National Library of

Medicine for public dissemination. For administrative purposes, please designate this submission, “SPL for approved NDA 22-363.”

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22-363.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

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.

We are waiving the pediatric study requirement for this application because this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is not likely to be used in a substantial number of pediatric patients.

POSTMARKETING REQUIREMENTS (PMRs) UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of increased pitavastatin exposure in patients with severe renal impairment or in patients being co-administered the combination of lopinavir and ritonavir that may predispose these patients to myopathy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of increased pitavastatin exposure in patients with severe renal impairment, or in patients being co-administered the combination of lopinavir and ritonavir, that may predispose these patients to myopathy.

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1501-1. A clinical trial to assess the effect of severe renal impairment on pitavastatin pharmacokinetics.

The timetable you submitted on July 27, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	October 30, 2009
Study Completion Date:	October 30, 2010
Final Report Submission:	December 31, 2010

1501-2. A drug-drug interaction clinical trial to examine the effect of the combination of lopinavir/ritonavir on pitavastatin Cmax and AUC.

The timetable you submitted on July 27, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	October 30, 2009
Study Completion Date:	October 30, 2010
Final Report Submission:	December 31, 2010

Submit the protocols to your IND, with a cross-reference letter to this NDA. Please use the above PMR numbers (1501-1 and 1501-2), as appropriate, in any submission regarding these PMRs. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii), requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

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

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

MISCELLANEOUS

Sufficient stability data have been submitted to support a 24-month expiration date for blister presentations, and a 36-month expiration date for 90-count bottles of the 1-, 2-, and 4-mg tablets.

We note the chemistry, manufacturing, and controls postmarketing agreement that was described in your amendment dated July 6, 2009.

NDA 22-363 was not referred to an advisory committee for review. Because pitavastatin is the eighth statin approved and there were no new significant efficacy or safety issues identified during the review of the application, other than those already identified for the statin drug class, an advisory committee meeting was not considered necessary.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:

Physician package insert

Carton and immediate-container labeling:

- 2 mg blister card
- 2 mg blister carton
- 4 mg blister card
- 4 mg blister carton
- 1 mg bottle label (90-count)
- 2 mg bottle label (90-count)
- 4 mg bottle label (90-count)