

# KOWA



RESEARCH INSTITUTE, INC.

ORIGINAL

*NDA 22-363*

RECEIVED

JUN 09 2009

CDR

June 9, 2009

Mary Parks, M.D., Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266  
**ATTN: Central Document Room**

ORIGINAL

**RE: NDA 22-363  
Pitavastatin (NK-104)  
Amendment #0033 to New Drug Application**

Dear Dr. Parks:

Kowa Company Limited (KCL) submitted its initial New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) dated October 1, 2008.

An initial safety report (A20090445-001) for a case of neoplasm of appendix was submitted to IND 60,492 for NK-104 (pitavastatin) on June 4, 2009 (IND serial #0133). The event occurred with Livalo, the marketed pitavastatin product in Japan.

The same IND submission (#0133) contains a follow-up report for A20090208 for which the initial report was submitted to this pending NDA in Amendment #0028 dated April 30, 2009. This case is now considered unrelated to pitavastatin.

A copy of the IND submission containing the CIOMS report and analysis of similar events for A20090445-001 and the follow-up CIOMS report for A20090208-003 is being submitted to pending NDA 22-363 at the suggestion of the Division.

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This amendment to NDA 22-363 consists of 1 CD, totaling less than 0.5 gigabytes. The submission is virus free. The following was used to check the files for viruses:

Trend Micro OfficeScan  
Version 8.0  
Virus Definitions: 6.173.00, created June 5, 2009

Sincerely yours,

A handwritten signature in cursive script that reads "Ross S. Laderman".

Ross S. Laderman, MPH  
Senior Director, Regulatory Affairs  
Kowa Research Institute, Inc.  
(U.S. Agent for Kowa Company Limited)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

7/8/09

DATE: July 8, 2009

TO: Mary H. Parks, M.D.  
Director  
Division of Metabolism and Endocrinology Products  
(DMEP)

FROM: John A. Kadavil, Ph.D.  
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.  
Associate Director - Bioequivalence  
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-363, Livalo  
(Pitavastatin [NK-104]) Tablets, 1 mg, 2 mg, and  
4 mg, Sponsored by Kowa Research Institute Inc.

At the request of the DMEP, the Division of Scientific Investigations conducted an audit of the clinical and analytical portions of the following bioequivalence study supporting NDA 22-363:

**Study Number:** NK-104-1.37US

**Study Title:** "Single-Dose, Randomized, Open-Label, Crossover, Bioequivalence Study of Pitavastatin 2-mg and 4-mg Tablets Manufactured by SkyePharma, France, and Pitavastatin 2-mg and 4-mg Tablets Manufactured by Patheon, USA, in Healthy Volunteers"

The clinical portion of study NK-104-1.37US was conducted at (b)(4). The analytical portion was conducted at (b)(4).

Following the inspection at (b)(4) (May 7 through May 14, 2009), no Form FDA-483 was issued. Following the inspection at (b)(4) (June 29 - July 3, 2009),

Page 2 - NDA 22-363, Livalo (Pitavastatin [NK-104])  
Tablets, 1 mg, 2 mg, and 4 mg

Form FDA-483 was issued. The observation and our  
evaluation are as follows:

(b) (4)

1. The firm failed to provide adequate documentation and objective criteria to justify the reintegration of 11 analytical run batches.

For those 11 runs, the decision to reintegrate and the reasons for reintegration were documented on the results tables. Since these results tables list the concentration values of calibrators and quality control (QC) samples, there is no assurance that the analyst decided to reintegrate **before** regression analysis and without viewing the concentrations. Thus, the reintegrations risk bias to run acceptance/rejection decisions.

Per the firm's documentation, reasons for reintegration included unacceptable integration of calibrators, study samples, and in one instance a low QC sample.

Additionally, the firm's standard operating procedure (SOP) for chromatography assessment (SOP# ETU/BIO/005) did not provide objective criteria for reintegration procedures.

At the close of the inspection, the firm indicated that they would provide a written response to the agency with a revised SOP. The response has not arrived as of this writing.

**Conclusion:**

It is objectionable that the firm failed to establish objective procedures for chromatogram reintegration in their documentation and SOP. However, records for both the original and reintegrated runs were maintained. DSI's evaluation of the original and reintegrated runs indicates minimal impact on study outcome.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

John A. Kadavil, Ph.D.  
Pharmacologist

Page 3 - NDA 22-363, Livalo (Pitavastatin [NK-104])  
Tablets, 1 mg, 2 mg, and 4 mg

**Final Classification:**

(b) (4)



cc:

HFD-48/Kadavil/Rivera-Lopez/CF  
OND ODEII DMEP/Johnson  
HFR-SW1540/Martinez/Cervantes (BIMO)  
HFR-SW150/Teitell (DIB)  
HFR-SW1575/Lorenz (ORA Investigator at (b) (4))  
Draft: JAK 7/8/09  
Edit: MFS 7/8/09  
DSI: (b) (4) O:\BE\EIRCover\22363kow.pit.doc  
FACTS (b) (4)

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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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John Kadavil  
7/8/2009 04:16:14 PM  
PHARMACOLOGIST

Michael Skelly  
7/8/2009 04:25:50 PM  
PHARMACOLOGIST  
MF Skelly signed for Dr. Viswanathan, in the absence  
of Dr. Yau.

## ORIGINAL

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JUL 10 2009

CDR

July 7, 2009

Mary Parks, M.D., Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266  
**ATTN: Central Document Room**

*N006 BM*  
ORIG AMENDMENT

**RE: NDA 22-363  
Pitavastatin (NK-104)  
Amendment #0036 to New Drug Application**

Dear Dr. Parks:

Kowa Company Limited (KCL) submitted its initial New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) dated October 1, 2008.

A June 29, 2009 e-mail from Dr. Iffat Chowdhury requested the following:

Please provide additional information (subject ID#, CRFs, narratives, etc.) on the subjects reported to have renal failure/ renal failure chronic/ renal insufficiency for pitavastatin. These subjects are listed in Table 2.7.4.111 and 2.7.4.107.

A response to this question was provided to Dr. Chowdhury in several e-mails on July 1, 2009. The formal NDA response to this request is now presented in the Appendix to this cover letter.

RESEARCH INSTITUTE, INC.

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Sincerely yours,



Ross S. Laderman, MPH  
Senior Director, Regulatory Affairs  
Kowa Research Institute, Inc.  
(U.S. Agent for Kowa Company Limited)

# KOWA



RESEARCH INSTITUTE, INC.

July 7, 2009

Mary Parks, M.D., Director  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266  
**ATTN: Central Document Room**

**RE: NDA 22-363  
Pitavastatin (NK-104)  
Amendment #0036 to New Drug Application**

Dear Dr. Parks:

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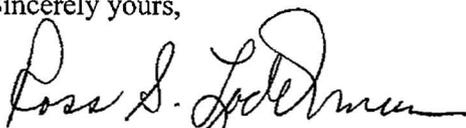
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Sincerely yours,



Ross S. Laderman, MPH  
Senior Director, Regulatory Affairs  
Kowa Research Institute, Inc.  
(U.S. Agent for Kowa Company Limited)

## Johnson, Kati

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**From:** Greeley, George  
**Sent:** Tuesday, July 07, 2009 3:22 PM  
**To:** Johnson, Kati  
**Subject:** Stowe, Ginneh D.  
NDA 22-363 Livalo  
**Importance:** High

Hi Kati,

The Livalo (pitavastatin) full waiver was reviewed by the PeRC PREA Subcommittee on April 22, 2009. The Division recommended a full waiver because 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. The PeRC agreed with the Division to grant a full waiver for this product.

Thank you.

George Greeley  
Regulatory Health Project Manager  
Pediatric and Maternal Health Staff  
Office of New Drugs  
FDA/CDER  
10903 New Hampshire Ave.  
Bldg #22, Room 6467  
Silver Spring, MD 20993-0002  
1.796.4025

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