

KOWA



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January 23, 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
NK-104 (pitavastatin)
Amendment #0007 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. The original application contains draft carton and container labels (Module 1.14.1.1) and draft labeling text (Modules 1.14.1.2 and 1.14.1.3).

This amendment contains revisions to the 3 modules cited above is to respond to the following requests to Kowa from the Division as identified below:

- An e-mail dated 11/14/2008 from Kati Johnson stating:
"The DMETS folks want color mock-ups of the bottle/cartons. They will review just the text, because the marketing folks do lots of subliminal advertising with graphics and color and text."
- The FDA filing communication from Dr. Parks dated 12/15/2008, specifically item #1 stating:
"Because the dosage strengths are based on the free base pitavastatin, the established name of your product is "pitavastatin". Revise all labeling, where applicable, to replac^{(b) (4)} with the correct established name "pitavastatin".

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Module 1.14.1.1 now contains mockups of carton and container labels that are near final for the finished product. They incorporate suggestions by the chemistry reviewer to address the proper use of the established name. Modules 1.14.1.2 and 1.14.1.3 contain revised draft labeling to reflect the proper established name, planned bottle size and also update some section texts resulting from internal corporate discussions.

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 7.3
Virus Definitions: 5.769.00, created January 13, 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)

January 20, 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
NK-104 (pitavastatin)
Amendment #0006 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.

This amendment is to respond to a request for information received by Kowa via e-mail on 12/30/2008 from the Division (Kati Johnson) as stated below:

In order for the QT IRT to review a **Thorough QT Study Report**, and to accelerate the review process, the following items should be submitted at the same time as the consult request:

- Electronic or hard copy of the study report
- Electronic or hard copy of the clinical protocol
- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- Copies of the study reports for any other clinical QT study for this product that has been performed
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- SAS code for the primary statistical analysis

- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study.
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below) – to be provided by sponsor.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose Include maximum proposed clinical dosing regimen
 Maximum tolerated dose Include if studied or NOAEL dose
 Principal adverse events Include most common adverse events; dose limiting adverse events
 Maximum dose tested Single Dose Specify dose
 Multiple Dose Specify dosing interval and duration
 Exposures Achieved at Maximum Tested Dose Single Dose Mean (%CV) C_{max} and AUC
 Multiple Dose Mean (%CV) C_{max} and AUC
 Range of linear PK Specify dosing regimen
 Accumulation at steady state Mean (%CV); specify dosing regimen
 Metabolites Include listing of all metabolites and activity
 Absorption Absolute/Relative Bioavailability Mean (%CV)
 T_{max} • Median (range) for parent
 • Median (range) for metabolites
 Distribution V_d/F or V_d Mean (%CV)
 % bound Mean (%CV)
 Elimination Route • Primary route: percent dose eliminated
 • Other routes
 Terminal t_{1/2} • Mean (%CV) for parent
 • Mean (%CV) for metabolites

CL/F or CL Mean (%CV)
 Intrinsic Factors Age Specify mean changes in Cmax and AUC
 Sex Specify mean changes in Cmax and AUC
 Race Specify mean changes in Cmax and AUC
 Hepatic & Renal Impairment Specify mean changes in Cmax and AUC
 Extrinsic Factors Drug interactions Include listing of studied DDI studies with mean changes in Cmax and AUC
 Food Effects Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
 Expected High Clinical Exposure Scenario Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.

The information requested by the FDA above is repeated below along with Kowa comments (bold italics) to assist with the QT consult.

- Electronic or hard copy of the study report
 - ***Kowa: Can be found in the original Module 5.3.4.1.1. An extra copy is included in this amendment***
- Electronic or hard copy of the clinical protocol
 - ***Kowa: Can be found in section 16.1.1 of CSR, original Module 5.3.4.1.1. A copy is included in the CSR in this amendment***
- Electronic or hard copy of the Investigator's Brochure
 - ***Kowa: A copy is included in Module 1.14.4.1 in this amendment***
- Annotated CRF
 - ***Kowa: A copy is included in this amendment in Module 5.3.4.1.1.***
- Copies of the study reports for any other clinical QT study for this product that has been performed
 - ***Kowa: No other QT studies for this product have been conducted.***
- A Define file which describes the contents of the electronic data sets
 - ***Kowa: File is included in SAS data sets for Module 5.3.4.1.1 in this amendment***
- Electronic data sets as SAS transport files
 - ***Kowa: File is included in SAS data sets for Module 5.3.4.1.1 in this amendment***
- SAS code for the primary statistical analysis
 - ***Kowa: File is included in SAS data sets for Module 5.3.4.1.1 in this amendment***

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- Data set whose QT/QTc values are the average of the replicates
 - ***Kowa: File is included in SAS data sets for Module 5.3.4.1.1 in this amendment***
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
 - ***Kowa: File is included in SAS data sets for Module 5.3.4.1.1 in this amendment***
- Narrative summaries and case report forms for any of the following that occur in this thorough QT study:
 - i. Deaths – ***Kowa: None***
 - ii. Serious adverse events - ***Kowa: None***
 - iii. Episodes of ventricular tachycardia or fibrillation - ***Kowa: None***
 - iv. Episodes of syncope - ***Kowa: None***
 - v. Episodes of seizure - ***Kowa: None***
 - vi. Adverse events resulting in the subject discontinuing from the study – ***Kowa: one AE on Page 75, section 12.3.2 of CSR (Module 5.3.4.1.1); copy included in this amendment***
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - ***Kowa: sent to ECG Warehouse upload ID 20090106143757***
- A completed Highlights of Clinical Pharmacology Table (Table 1 shown below) – to be provided by sponsor.
 - ***Kowa: A copy is included in Module 5.3.4.1.1 in this amendment***

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 7.3

Virus Definitions: 5.769.00, created January 13, 2009

Sincerely yours,



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

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January 14, 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
NK-104 (pitavastatin)
Amendment 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.

This amendment is to respond to a request for information received by Kowa via e-mail on January 6, 2009 from Dr. Iffat Chowdhury as identified below:

Would it be possible for Kowa to do a subanalysis of the subjects taking the 4 mg dose in LIVS-01? This would be of the approximately 186 subjects identified in the registry. We are specifically interested in the following adverse events terms:

Specific events under Musculoskeletal and Connective Tissue Disorders: Myalgia, Muscle spasms, Muscular weakness, Arthralgia, Musculoskeletal stiffness, Back pain, Pain in extremity, Myopathy, Musculoskeletal pain, Neck pain, Osteoarthritis, Rhabdomyolysis, Arthritis, Joint swelling, Blood creatinine phosphokinase increased, Myoglobin urine present, Myoglobin blood increased.

Under Hepatobiliary disorders: Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma glutamyl transferase increased, Hepatic function abnormal, Liver disorder, Jaundice, Jaundice cholestatic, Blood alkaline phosphatase increased, Blood bilirubin increased.

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Under Renal and Urinary disorders: Proteinuria, Haematuria, Renal failure, Blood creatinine increased, Protein urine present.

The table generated to respond to this inquiry contains the full extent of all adverse drug reactions reported in the 4 mg group in the LIVS-01 study. Those categories identified in Dr. Chowdhury's request which do not appear were not reported.

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 7.3
Virus Definitions: 5.763.00, created January 11, 2009

Sincerely yours,



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



DEPARTMENT OF HEALTH & HUMAN SERVICES

1/5/09
Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-363

KOWA Research Institute, Inc
Attention: Ross Laderman
Sr. Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Please refer to your pending New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Livalo (pitavastatin) Tablets, 1 mg, 2 mg, and 4 mg.

We have completed our preliminary review of the clinical pharmacology section of your application. We have the following comments and recommendations:

- A. It contains results from Protocol NK-104-109, entitled "An Open-Label Study on the Pharmacokinetics of Pitavastatin (NK-104) when Administered Concomitantly with Fenofibrate or Gemfibrozil in Healthy Volunteers". (b) (4), performed the bioanalytical analyses for pitavastatin and pitavastatin lactone in plasma and urine samples.

Since 2000, FDA has conducted several comprehensive inspections of bioequivalence studies in which the bioanalytical analysis was conducted by (b) (4)

(b) (4) The findings of these inspections raise significant concerns about the validity of the reported results of these analytical studies conducted in support of drug applications for marketing. Our findings from these inspections include, but are not limited to, the following:

- Failure to conduct a systematic and thorough evaluation to identify and correct sources of contamination.
- Failure to investigate anomalous results.
- Lack of assay reproducibility between original and repeat results.
- Assay accuracy not assured under the conditions of sample processing.
- Biased exclusion of study data resulting in the acceptance of failed runs.
- Failure to demonstrate the accuracy of analytical methods with appropriate validation experiments and documentation.

As a result of these findings, (b) (4) agreed to conduct an audit of data from all its bioequivalence studies generated from January 2000 to December 2004. However, FDA identified significant deficiencies with the (b) (4) audit during its most recent inspection. Thus, serious questions remain about the validity of any data generated by (b) (4) in studies during this time period that have not been inspected by FDA.

If you intend to make labeling claims for the interaction results between pitavastatin and fenofibrate plus gemfibrozil, you should do one of the following, in order of preference:

1. Repeat the pitavastatin and fenofibrate plus gemfibrozil interaction study.
 2. Re-assay the samples for pitavastatin and pitavastatin lactone at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period.
 3. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of human drug interaction studies and bioanalytical data, and is selected by your company rather than by (b) (4), to verify the results obtained by (b) (4)
- B. Pitavastatin is a 3R- and 5S- specific stereoisomer. You should provide data to demonstrate whether pitavastatin shows any chiral conversion via metabolism.
- C. For Study NK-104-1.37US, entitled "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", you should submit plasma pitavastatin and pitavastatin lactone concentration data as well as their pharmacokinetic parameters in SAS XPT files or advise the location of such electronic data.

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

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Eric Colman
1/5/2009 09:37:59 AM
Eric Colman for Mary Parks