KOWA

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ORIGINAL

N-000-BC
ORIG AMENDMENT

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APR 03 2009
CDR

April 1, 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 #0023 to New Drug Application**

N-000-BC

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 following chemistry comments were sent to Kowa in a March 11, 2009 e-mail from Kati Johnson:

1. Provide a written assurance that final granulate blend content uniformity testing will be omitted only if the nine process validation batches manufactured in 2009 satisfy the Draft Guidance for Industry (Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment" dated October 2003.
2. The RSD of the pitavastatin peak areas for the system suitability for Method 850510 (Pitavastatin Related Substances) is (b)(4), while the analogous value for the Assay and Identification method is (b)(4). Why aren't both values (b)(4)?
3. Specify the lot number of the 1 mg tablets used in the drug product dissolution method validation.
4. Confirm your intention to continue stability testing in the (b)(4) bottle configuration following your original submission.
5. The applicant is reminded to submit the 12-month stability data on the primary batches.

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6. Provide a comparison or justification that bridges the stability data between the supportive and primary stability batches. The submission should include, but not be limited to the following: 1.) a comparison of the materials used in blister and bottle configurations, 2.) an explanation of the difference in the blister container configurations for the supportive and primary stability trials; the blister container closure configurations for the supportive and commercial configurations are described as (b) (4) and (b) (4) foil lidding, respectively, and 3) a comparison of the headspace for the (b) (4) 90-count bottle configurations.
7. Provide justification and data that supports the label claim that pitavastatin is freely soluble in chloroform & dilute hydrochloric acid and sparingly soluble in octanol.
8. Pitavastatin solubility in ethanol should be classified as slightly soluble.
9. Provide a scale for the final color mock-ups of planned labeling.

We have responded to these questions in the Appendix and, where appropriate, we have enclosed an updated Module 3 and/or Module 2 section. Our responses draw reference to these sections. In all there are ten updated sections in this submission. The following eight sections are relevant to the above CMC comments/requests:

| | |
|---|---|
| 3.2.P.2.1 | 3.2.P.8.3 |
| 3.2.S.1.3 | 3.2.P.2.4 |
| 2.3.P | 3.2.P.5.2 |
| 2.3.S.1 | 3.2.P.8.1 |

In addition we are submitting revisions of the following two sections to correct an error in the original NDA submission: 3.2.S.4.1 and 3.2.S.4.2. The original application contained a microbial limits test specification and procedure for the drug substance (API) following receipt by the drug product manufacturer, Patheon, Inc. The microbial limit test for the drug substance is conducted by the API manufacturer, (b) (4) and the result is recorded on a certificate of analysis (COA) that accompanies the shipment. That test result for the microbial limits on the COA is used as acceptance criteria by (b) (4).

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: 5.8881.00, created March 4, 2009

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.

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MAR 11 2009
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March 11, 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**

ORIG AMENDMENT

**RE: NDA 22-363**
**Pitavastatin (NK-104)**
**Amendment #0020 to New Drug Application**

N000-BS

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.

In a February 26, 2009 e-mail Dr. Chowdhury made the following request to Kowa:

> Would Kowa be able to re-analyze Table 2.7.4.152 in Section 2.7 Clinical Summary to include Caucasian and Asian+ Indian patients on placebo?

It was subsequently agreed with Dr. Chowdhury that Kowa would provide the analysis based on Group 1 rather than Group3 that was identified in Table 2.7.4.152. The Clinical Summary table cited by Dr. Chowdhury was an in-text table created by medical writers rather than one programmed by our statistical group. Therefore we have had the statistical group program the enclosed 4 new tables that update the Clinical Summary table 2.7.4.152 for Group 1 (instead of Group 3). These tables, numbered 1.4.2.1, 1.4.2.2, 1.4.2.3 and 1.4.2.4, appear in the Appendix to this cover letter since, as stand-alone data, they have no other location in the prescribed CTD hierarchy.

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Sincerely yours,

Ross S. Laderman, MPH
Senior Director, Regulatory Affairs
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# KOWA

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Kowa

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MAR 11 2009
CDR

March 11, 2009

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

N 000-02
ORIG AMENDMENT

**RE: NDA 22-363**
**Pitavastatin (NK-104)**
**Amendment #0022 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.

In a February 24, 2009 e-mail Dr. Chowdhury made the following request of Kowa:

> I have another request for Kowa. Would the company be able to conduct a demographic analysis on the 37 post marketing cases of rhabdomyolysis in Japan? Specifically, I am interested in the age, sex, Creatinine Clearance, CPK level, and pitavastatin dose. I am also interested in the co-morbid conditions such as diabetes, hypertension, and cardiovascular heart disease in these patients. It would be very helpful if this information could be provided in table format.

In response to this request we have generated the five enclosed tables. The information in these tables has been updated and Table 5 reflects changes in diagnoses from those previously reported due to receipt of follow-up CIOMS reports. These tables are presented in the Appendix to this cover letter since, as stand-alone data, they have no other location in the prescribed CTD hierarchy.

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Mary Parks, M.D., Director
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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 #0021 to New Drug Application**

N000-BM

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.

In a February 27, 2009 e-mail Dr. Chowdhury made the following request of Kowa:

> Thanks for Kowa's submission on January 26, 2009 of the 29 patients with CPK elevations >10XULN. Would Kowa analyze those patients for the following: Age (Mean +/- SD), Sex, Baseline (Mean +/- SD) LDL, CPK, Cr, presence of cardiovascular heart disease, hypertension, diabetes, and dose of pitavastatin in a table format? Please separate the 9 cases of rhabdomyolysis in a separate row in this table.

In response to this request we have generated the 3 enclosed tables numbered 1.3.1, 1.3.2 and 1.3.3. Note that we do not have "history of CHD" in the integrated ISS datasets. It was not collected in the Phase II study CRFs. The 3 tables separately include cases with rhabdomyolysis and without rhabdomyolysis. These tables are presented in the Appendix to this cover letter since, as stand-alone data, they have no other location in the prescribed CTD hierarchy.

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KOWA

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MAR 10 2009
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ORIGINAL
N.000-BL

March 10, 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 #0019 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.

Amendment #0007 contained revised labels proposed for the 1 mg, 2 mg and 4 mg commercial bottles of pitavastatin tablets. That amendment also contained the proposed blister card label and box for the professional sample size of pitavastatin tablets. This amendment contains a final revision for the professional blister card and box only. The revision and clarification regarding the blister card as well as scanned examples of the blister card itself are contained in Module 1.14.1.1 in this amendment.

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Sincerely yours,

Ross S. Laderman, MPH
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