

KOWA



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May 5, 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 #0029 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 February 11, 2009 request for information received by Kowa via e-mail from the Division (Dr. Iffat Chowdhury) as identified below:

First, would you be able to generate a table with the weeks of exposure to pitavastatin by age group (>65 or <65) and by dose (1 mg to 4 mg), or let me know the location of the table if it's already submitted?

Second, I'm still interested in knowing the rhabdomyolysis rate for pitavastatin in Japan. I know we exchanged email in January on this topic. In this pitavastatin NDA, there were 37 cases of rhabdomyolysis identified in Japan with all the marketed doses. It would be very helpful to the review if Kowa could submit data that would put this number in context. The rhabdomyolysis reporting rates per XXX,XXX of prescription dispensed in Japan in six month intervals has been submitted to the Agency for another product marketed in Japan. Thus, I know it is possible to obtain this information.

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The enclosed Modules 5.3.5 and 5.3.6 respond respectively to each of Dr. Chowdhury's 2 inquiries.

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: 6.103.00, created April 30, 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)

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April 30, 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

N-000 (Bm)
ORIG AMENDMENT

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APR 30 2009

CDER CDR

**RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0028 to New Drug Application**

N-000 Bm

Dear Dr. Parks:

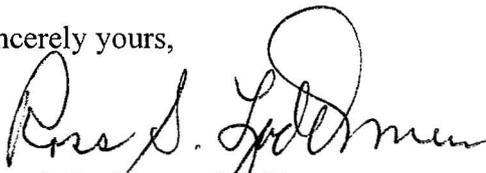
Kowa Company Limited (KCL) submitted its initial New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) dated October 1, 2008.

An initial safety report (A20090208-001) for a case of erythema multiforme exudativum was submitted to IND 60,492 for NK-104 (pitavastatin) on April 28, 2009 (serial number 0132). The event occurred with Livalo, the marketed pitavastatin product in Japan. A copy of the IND submission (enclosed) containing the CIOMS report and analysis of similar events is also being submitted to pending NDA 22-363 at the suggestion of the Division.

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
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Virus Definitions: 5.993.00, created April 28, 2009

Sincerely yours,



Ross S. Laderman, MPH
Senior Director, Regulatory Affairs
Kowa Research Institute, Inc.
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Subjects Observed With	Drug/Dose	Drug/Dose
≥ 3 XULN		
≥ 3 XULN, Consecutive		
≥ 5 XULN		
≥ 10 XULN		

Each subject listed in this table is presented only once, in the category of the highest activity level reported.

- 1 ULN = Upper limits of normal.
- 2 Consecutive: This category includes those subjects with two consecutive measurements for ALT and/or AST ≥ 3 xULN, single, last measurement ≥ 3 xULN, or
- 1 a measurement ≥ 3 xULN followed by a measurement < 3 xULN that was
- 2 taken more than 2 days after the last dose of study medication.

In response to this request we have generated a number of tables. These tables are presented in the Appendix to this cover letter (following each of the four repeated requests above) since, as stand-alone data, they have no other location in the prescribed CTD hierarchy. In addition a SAS transport data file that includes the unscheduled visits described in request #1 and #4 is also included 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 8.0
Virus Definitions: 5.983.00, created April 23, 2009

Sincerely yours,



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

ORIGINAL

April 30, 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

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APR 29 2009

CDR

N000-BM

**RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0027 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 March 25, 2009 e-mail from Kati Johnson conveyed the following request from Dr. Chowdhury:

Regarding Kowa's March 6, 2009 submission to NDA 22-363, please note that the *Concept Paper on Premarketing Evaluation of Drug-Induced Liver Injury* specifies that unscheduled laboratory evaluations should be included in the database. Therefore, this clinical reviewer requests the following:

1. Submit a dataset with all the ALT, AST and CK lab values including values from unscheduled visits or hospitalizations outside of the study sites.
2. Submit an analysis of time to onset of aminotransferase elevation for patients on pitavastatin (median number of days, mean number of days, standard deviation).
3. Demographic analysis of patients with aminotransferase elevations including age, sex, weight in kg, baseline creatinine, percent baseline >1XULN.
4. Submit an analysis (including unscheduled visits) of single as well as consecutive elevations in ALT and AST for all doses of pitavastatin and comparator drugs. A definition of consecutive and an example of such an analysis follows:

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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: 5.977.00, created April 20, 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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APR 24 2009

CDR

April 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
Pitavastatin (NK-104)
Amendment #0026 to New Drug Application**

N 000-BC
ORIG AMENDMENT

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 April 9, 2009 e-mail from Kati Johnson the following request from the Chemistry reviewer was transmitted:

I'm trying to establish an expiry period for the 1 mg tablet in 90-count HDPE bottle configuration. It would be helpful if the applicant could provide the 12-month long-term stability data for Batch 3066107 as soon as possible. This stability study was initiated April 1, 2008, so I don't know how quickly they can turn around that data. Could you please send an information request for that stability data and an estimation of when we might receive that data?

Enclosed is a revised stability Table 3.2.P.8.3.1-2 for Batch # 3066107 with data updated to include 12-month long term stability. This table was also sent to Kati Johnson via e-mail on April 17, 2009. In addition we are submitting complete revised Modules 3.2.P.8.1 and 3.2.P.8.3 to reflect this updated data.

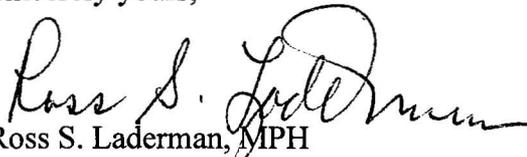
This amendment to NDA 22-363 consists of 1 CD, totaling less than 0.5 gigabytes. The submission is virus free. The following was used to check the files for viruses:

Trend Micro OfficeScan

Version 8.0

Virus Definitions: 5.921.00, created March 25, 2009

Sincerely yours,



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

April 16, 2009

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

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1 APR 20 2009

CDR

ORIG AMENDMENT

**RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0025 to New Drug Application**

N000 BM

ORIGINAL

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 March 26, 2009 e-mail Dr. Chowdhury made the following request of Kowa:

Please submit all the postmarketing serious Hepatobiliary cases, including elevated aminotransferase from July 2003 to July 2008 from Japan. I understand this to be a total of 43 cases (40 from the original NDA submission and 3 in the 4-month safety update). Although Table 2.7.4.200 in the Clinical Summary gives a short description of 40 of those cases, it is not adequate. Please give priority to those 7 cases identified in Table 2.7.4.182 in the Clinical Summary with concurrent aminotransferase elevations and total bilirubin > 3mg/dL when submitting the full narrative. The initial ALP value should be included in the narrative.

In an April 1, 2009 e-mail from Ross Laderman of Kowa to Dr. Chowdhury it was explained that the narratives (CIOMS) from the 40 cases in the original NDA submission could be found in the NDA:

Your inquiry below is one of the two that we wanted to briefly discuss. Our concern is that the information you are requesting already exists in the NDA. Each listing in Table 2.7.4.200 is hyperlinked to a full CIOMS report (that includes the narrative) for that

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individual listing. The short description in this table is just that but you can reach all the expanded information by clicking on the link with the mouse. So the individual narratives you are requesting are already there.

The seven cases identified in Table 2.7.4.182 are included in Table 2.7.4.200. They can easily be identified by looking at the column entitled "Bilirubin ADR Grade" and finding the cases for which the recorded grade is 2.

The only pieces that you do not already have are the CIOMS forms for the 3 cases identified in the 4-month safety update. Please let me know if you would like us to submit them. Otherwise please let me know if this explanation is satisfactory. There is no additional information on the 40 cases other than that already in the NDA.

Dr. Chowdhury subsequently requested the 3 additional CIOMS but upon further examination we discovered that, in fact, there were 7 CIOMS reports listed in the 4 month update that may fit this category. In addition to these we are enclosing 4 earlier CIOMS from Japan which were inadvertently not included in the European dossier, which served as a source for our NDA. These 11 CIOMS reports are included in the enclosed Module 5.3.6.21.

All original CIOMS reports from Japan may be seen in Module 5.3.6.18. Of note is that ELIVA5604 (A20080331) has since been downgraded and is no longer a serious ADR. Also ELIVA4882 (A20062305), which is referenced in Table 2.7.4.200, was subsequently downgraded; therefore the CIOMS was not submitted in our NDA.

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
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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)

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APR 15 2009

CDR

April 14, 2009

Mary Parks, M.D., Director
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5901-B Ammendale Road
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ORIGINAL

ORIG AMENDMENT

**RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0024 to New Drug Application**

N-000-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 an April 7, 2009 e-mail from Kati Johnson the following request from Manoj Khurana was transmitted:

There is one Phase IIb study (Study No. NKS104A2204) where sponsor collected samples for drug concentration measurement over 12 week trial duration. Also Section 10.6 of this study report provide some information on sponsors attempt to draw exposure-response relationship. Here is a draft list of SAS data sets that we can request for this study to explore further:

- (1) PK (Including but not limited to following columns: SUBID, TRT, VISIT, TIME, CONC, ITT, PP, COMPLETE)
- (2) DEMOGRAPHICS (Including but not limited to following columns: SUBID, TRT, AGE, SEX, WT, BMI, HT, RACE, ITT, PP, COMPLETE)

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- (3) EFFICACY (LDL, HDL etc)
- (4) ADVERSE EVENTS
- (5) LAB (Including but not limited to following columns: SUBID, TRT, VISIT, TIME, LAB PARAMETER, LAB VALUE, RANGE, FLAG (high/low, >ULN etc), ITT, PP, COMPLETE); We need the comprehensive data set that includes all laboratory measurements (e.g. AST, ALT, CK etc).

Could you also ask the project manager to include a general statement that sponsor is encouraged to provide additional data sets for this trial, similar to what they have submitted for the controlled clinical trials.

In response to this request we are submitting the entirety of the datasets for this trial which was conducted by (b) (4). Please find enclosed the raw data and derived data for NKS-104A2204 as provided by (b) (4). We have also included an annotated CRF to help identify the variables in the raw data, and a RAMP document (dataset specifications) supplied by (b) (4) to use with the derived datasets.

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
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Virus Definitions: 5.955.00, created April 8, 2009

Sincerely yours,



Ross S. Laderman, MPH
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