

(a) Myalgia Overall

Treatment	n _{AE} /n	AE %	Odds ratio	95% CI	p-value
NK-104-301					
Pitavastatin 2 mg	5/317	1.6%	1.6	[0.178, 77.3]	1
Atorvastatin 10 mg	1/102	1.0%			
Pitavastatin 4 mg	6/298	2.0%	2.1	[0.247, 96.39]	0.6837
Atorvastatin 20 mg	1/102	1.0%			
NK-104-302					
Pitavastatin 2 mg	9/305	3.0%	1.6	[0.319, 15.26]	0.736
Simvastatin 20 mg	2/106	1.9%			
Pitavastatin 4 mg	6/315	1.9%	0.68	[0.142, 4.277]	0.6992
Simvastatin 40 mg	3/108	2.8%			
NK-104-304-309					
Pitavastatin 4 mg	12/235	5.1%	0.60	[0.231, 1.612]	0.2544
Simvastatin 40 mg	10/122	8.2%			
NK-104-305-310					
Pitavastatin 4 mg	16/281	5.7%	2.7	[0.757, 14.77]	0.1349
Atorvastatin 20 mg	3/138	2.2%			
NK-104-306					
Pitavastatin 1 mg	3/209	1.4%	0.49	[0.064, 3.699]	0.4004
Pravastatin 10 mg	3/103	2.9%			
Pitavastatin 2 mg	3/252	1.2%	2.4	[0.509, 22.7]	0.358
Pravastatin 20 mg	3/102	2.9%			
Pitavastatin 4 mg	3/210	1.4%	0.48	[0.063, 3.645]	0.3967
Pravastatin 40 mg	3/102	2.9%			

(b) POSSIBLE DRUG RELATED HEPATIC DISORDERS

Treatment	n _{AE} /n	AE %	Odds ratio	95% CI	p-value
NK-104-301					
Pitavastatin 2 mg	4/317	1.3%	NA	[0.2119, +Inf]	0.5763
Atorvastatin 10 mg	0/102	0%			
Pitavastatin 4 mg	3/298	1.0%	NA	[0.141, +Inf]	0.5736
Atorvastatin 20 mg	0/102	0%			
NK-104-302					
Pitavastatin 2 mg	8/305	2.6%	0.6823	[0.096, 7.644]	0.6479
Simvastatin 20 mg	0/106	0%			
Pitavastatin 4 mg	3/315	1.0%	NA	[0.597, +Inf]	0.1196
Simvastatin 40 mg	2/108	1.9%			
NK-104-304-309					
Pitavastatin 4 mg	2/235	0.9%	0.516	[0.037, 7.2]	0.6085
Simvastatin 40 mg	2/122	1.6%			
NK-104-305-310					
Pitavastatin 4 mg	4/287	1.4%	0.982	[0.139, 10.98]	1
Atorvastatin 20 mg	2/141	1.4%			
NK-104-306					
Pitavastatin 1 mg	3/209	1.4%	NA	[0.2035, +Inf]	0.5534
Pravastatin 10 mg	0/103	0%			
Pitavastatin 2 mg	0/252	0%			
Pravastatin 20 mg	0/102	0%			
Pitavastatin 4 mg	1/210	0.5%	NA	[0.0124, +Inf]	1
Pravastatin 40 mg	0/102	0%			

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ORIGINAL

ORIGINAL AMENDMENT 0016-0000

March 6, 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 #0016 to New Drug Application**

N 000-BZ

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 20, 2009 e-mail Dr. Chowdhury made the following request of Kowa:

The pitavastatin NDA reports 40 subjects with significantly elevated AST and/or ALT elevations in the post marketing period in Japan:

It would be helpful if the subjects were summarized in a table with the specific laboratory elevation (ALT or AST not lumped together) by $\geq 5XULN$, $\geq 10XULN$, $\geq 20XULN$, $\geq 50XULN$, bilirubin elevation ($\geq 1.5XULN$, $\geq 2.0XULN$, $\geq 3.0XULN$), and alkaline phosphatase elevation $> 2XULN$ and by dose of pitavastatin.

Would the company also perform a demographic analysis of these 40 patients with transaminase elevations? Specifically, age, sex, weight, baseline creatinine clearance, percent baseline $> 1XULN$ in aminotransferase?

Would the company also perform a medical history analysis of these 40 patients by with diabetes, hypertension, cardiovascular heart disease, renal disease?

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Lastly, please conduct a time to event analyses of these 40 patients (range, median, mean, standard deviation).

We have generated 7 tables that respond to the various elements contained in the request. These are numbered 1 through 7 and the captions are self explanatory. These tables are provided in the Appendix to this letter since, as stand-alone data, they have no other location in the prescribed CTD hierarchy.

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: 5.875.00, created March 1, 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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ORIGINAL AMENDMENT

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March 6, 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 #0015 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 a February 19, 2009 e-mail Dr. Chowdhury made the following request of Kowa:

Would you provide us a table with single as well as multiple elevations in ALT and AST for all doses of pitavastatin (≥ 3 XULN, ≥ 3 XULN (multiple), ≥ 5 XULN, ≥ 5 XULN (multiple), ≥ 10 XULN, ≥ 10 XULN (multiple)) for the Group 1 and Group 3 analyses? If any of the elevations in liver transaminases were associated with CPK elevations, please indicate at which dose and how many patients.

We have generated the Group 1 and Group 3 tables requested and have also included patient data listings 2.1 and 2.3 that serve as the basis for the requested tables. This information is provided in the Appendix to this letter since, as stand-alone data, it has no other location in the prescribed CTD hierarchy.

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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: 5.875.00, created March 1, 2009

Sincerely yours,



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