KOWA

RESEARCH INSTITUTE, INC.

March 9, 2009

ORIG AMENDMENT

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

MAR 1 0 2009
CDR

RE: NDA 22-363
Pitavastatin (NK-104)
Amendment #0017 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 an e-mail from the Division dated March 3, 2009 Kowa received the following request:

> I checked with the Qtc folks, and they still need the following: "provide PR baseline value to the revised analysis dataset ANALYSIS.XPT dataset". This was NOT an omission on your part, as it was not requested of you in the initial e-mail……

We have previously submitted data on our QTc study in the original NDA and in Amendments #0006 and #0014. We are submitting the additional requested analysis in Module 5.3.4.1.1 in this amendment.

430 Davis Drive, Suite 200, Morrisville, North Carolina 27560 Telephone: 919.433.1600 Fax: 919.433.1620

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)

Pharmacology/Toxicology Mid-Cycle Deliverables

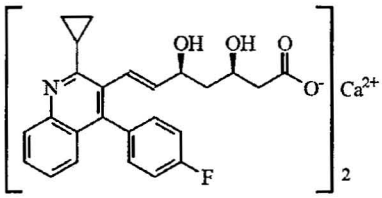
Mid-Cycle Deliverable	Goal Date	Status
Filing Review Meeting • **Deliverable: Regulatory history, summary of pharmacology and toxicology findings from preliminary review of existing data, adequacy of NDA submission**	**45- day of NDA submission**	Completed
Genetox Study Review (impurities and drug substance) • **Deliverable: Draft review, label recommendation/interact with genetox committee**	**2-3 months of NDA submission**	Gene-tox review is complete; pitavastatin is negative for genetox by weight of evidence approach, impurities qualification pending review
Carcinogenicity Study Review • **Deliverable: Identify statistical reviewer**	**1-month of NDA submission**	Dr. Min Min
• **Deliverable: Schedule ECAC meeting**	**1-month of NDA submission**	Meeting scheduled for April 7, 2009
• **Deliverable: Draft review of Carcinogenicity study with statistical input, *Interact with statistician***	**6-months of NDA submission**	**See attachment**
• **Deliverable: ECAC review of carcinogenicity study, incorporation of eCAC comments in the review, Identification of issues from Carcinogenicity study & related post marketing commitments, labeling recommendation**	**7- month of NDA submission**	Pending ECAC review
ReproTox Study Review (Seg III and I) • **Deliverable: Draft review, Identify issue/s (special studies for post marketing commitments), labeling recommendation, *Interact with Reprotox committee***	**5- month of NDA submission**	Review complete, sponsor seeking Category X labeling
Impurity/Extractable Qualification • **Deliverable: Begin review; *interact with CMC***	**3-month of NDA submission-will depend on CMC also**	Interacting with Olen Stephens, review in progress
• **Deliverable: Identify whether the impurities are qualified, Identify approvability/post marketing commitment issues**	**5-6 month of NDA submission-if sponsor has final formulation**	Sponsor has submitted studies to qualify the (b) (4) [redacted], but review not yet complete
Toxicokinetic Study Review • **Deliverable: Draft review; *Interact with Clinical Pharmacology* for dose and (b) (4) [redacted], *Interact with Medical Reviewer* for adverse event comparison and dose multiples**	**6- months of NDA submission**	Interacting with Johnny Lau on (b) (4) [redacted] concerns; will interact with Iffat Chowdhury on AE comparison and dose multiples
Chronic Toxicity Study Review • **Deliverable: Draft review**	**6- months of NDA submission**	Reviews basically complete, requires further integration
Pharmacology Study Review • **Deliverable: Draft review, identify PD issues**	**6- months of NDA submission**	Approximately 50% complete, will require integration
Tox findings compared in animal chronic studies and human phase 3 studies • **Deliverable: Input in ODS database**	**8- months of NDA submission**	Pending completion of comprehensive review

NDA 22-363
Pitavastatin
Kowa Company Limited
Mid-Cycle CMC Handout (3/09/09)

(b) (5)

Drug Substance:

The applicant has addressed all CMC comments in the 74-day letter.



Molecular formula: $C_{50}H_{46}CaF_2N_2O_8$

Molecular weight: 880.98

Pitavastatin Calcium: Physical-chemical Properties

(b) (4)

(5)

Drug Substance (DMF (b) (4) :

- Manufactured by (b) (4) . – DMF is adequate.
- 30 mo. long-term and 6 mo. accelerated stability data (b) (4) month retest period
- (b) (4) and (b) (4) are process impurities and not degradants. These impurities do not increase on storage or interconvert from the drug substance. The proposed limits for these impurities exceed the ICH Q3A qualification threshold for drug substance impurities. The non-clinical review team was alerted to these levels and has confirmed (2/19/2009 by email) that the applicant has attempted to qualify the impurities. The non-clinical reviewer will evaluate their studies to determine if the impurities have been adequately qualified.

Drug Product

Route of Administration	Oral
Dosage Form	Immediate release film-coated tablet (b) (5)
Packaging type	• 90-count (b) (4) bottles with CR lid (1 mg, 2 mg, and 4 mg) (b) (4) oil lidding for physician samples (b) (5)
Potency	1 mg, 2 mg, and 4 mg (dosage based on free base)

- Except for the color (b) (4) coating the tablets, all the excipients are pharmacopeial (USP/NF). The DMF for this excipient has been reviewed and found adequate.
- All dosage forms are dose proportional. All tablet strengths are manufactured from a (b) (4) blend.
- Tablets are white and debossed with "KC" and "1", "2", or "4" on reverse side.

Pitavastatin tablet formulations:

Component	Reference	Function	Quantity		
Tablet Core			**1 mg Tablet (mg)**	**2 mg Tablet (mg)**	**4 mg Tablet (mg)**
Pitavastatin (b) (4)	DMF (b) (4)	Active	1.0451	2.091	4.181
Lactose Monohydrate	NF	(b) (4)	(b) (4)		
Low Substituted Hydroxypropyl	NF				
Cellulose					
Hypromellose (b) (4)	USP				
Magnesium Aluminometasilicate (b) (4)	NF				
Magnesium Stearate	NF				
(b) (4)	USP				
(b) (4)					
Pitavastatin (b) (4)	DMF (b) (4)				
Film Coating (b) (4)					
(b) (4)	DMF (b) (4)				
(b) (4)	USP				
Total			**83**	**165**	**329**

Drug Product Internal Comments:

1. The Japanese product doses based on the salt and the US product doses on the free base; there will be a (b) (4) difference in the concentration of active ingredients in analogous tablets. Despite differences in tablet debossment, their size and coloring will make analogous tablets similar in appearance – is this a problem?
2. The dissolution method is discriminatory between 2 mg and 4 mg, but comparative data for the 1 mg has not been submitted. Only a Q = (b) (4) has been set for the 30 minute time point to support an immediate-release claim. A bioequivalency waiver has been requested for the 1 mg; we will not require a multi-point dissolution data for the 1 mg tablet if they are deemed bioequivalent.
3. Expiration date is still under review.

(b) (5)

Drug Product Comments and Questions for the Applicant:

1. The applicant is reminded to submit the 12-month stability data for your primary batches.
2. 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 (b) (4) foil lidding, respectively, and 3) a comparison of the headspace for the (b) (4) 1 90-count bottle configurations.

Labeling Comments for the Applicant:

1. Provide justification and data that supports the label claims that pitavastatin is freely soluble in chloroform & dilute hydrochloric acid and it is sparingly soluble in octanol. Also, pitavastatin solubility in ethanol should be classified as slightly soluble.
2. Provide a scale for the labels.

Biostatistics Mid-Cycle Deliverables

(1) Confirmation of sponsor's major conclusions or identification of statistical issues that might preclude approval.

- Confirmed sponsor's efficacy results.
- Performed subgroup analysis for each treatment-control pair. The sponsor's subgroup analyses examined only the Livalo arms and excluded control groups and therefore are not appropriate.
  I compared Livalo to the control arms for subgroup results. My results suggest no difference between Livalo and the active comparators in subgroup analysis of each study except a gender difference was found in **NK-104-305** (b) (5) [redacted]

  Pitavastatin 4 mg vs. Atorvastatin 20 mg, 95% CI: [-16.90, -1.19] (b) (5) [redacted]

Study NK-104_305 in subjects with type 2 diabetes was not non-inferiority.

Non-inferioprity margin: -6%

	Pitavastatin 4 mg QD	Atovastatin 20 mg QD
	FAS Population	
N	274	136
Baseline LDL-C Mean (SD)	142. 8 (27. 41)	146. 0 (26. 98)
Endpoint LDL-C Mean (SD)	84. 3 (31. 01)	82. 4 (27. 45)
Percent Change from Baseline to Endpoint Mean (SD)	−40. 78 (19. 599)	−43. 25 (16. 378)
Adjusted Mean Difference	2. 33	
Difference (95% CI)	(−1. 52, 6. 18)	
P-value	0. 235	
	COM Population	
N	248	124
Baseline LDL-C Mean (SD)	142. 4 (27. 23)	144. 3 (25. 66)
Week 12 LDL-C Mean (SD)	83. 0 (28. 47)	79. 5 (23. 80)
Percent Change from Baseline to Endpoint Mean (SD)	−41. 36 (18. 058)	−44. 59 (15. 331)
Adjusted Mean Difference	2. 76	
(95% CI)	(−0. 90, 6. 43)	
P-value	0. 139	
	PP Population	
N	214	107
Baseline LDL-C Mean (SD)	143. 6 (27. 71)	144. 3 (25. 70)
Week 12 LDL-C Mean (SD)	84. 0 (29. 63)	78. 4 (21. 32)
Percent Change from Baseline Mean (SD)	−41. 14 (18. 852)	−45. 01 (13. 981)
Adjusted Mean Difference	3. 72	
(95% CI)	(−0. 32, 7. 77;)	
P-value	0. 071	

(2) Discussions held with medical officer regarding statistical issues of concern to Dr. Iffat Chowdhury (such as secondary endpoints, important safety variables, etc.)

The sponsor listed descriptive AE Tables, such as the Table 2.7.4.152, without statistical analysis. AE analysis for the pair-wise treatments will be analyzed for the overall population and subgroup (age, race, gender) for three AE categories:

(a) RHABDOMYOLYSIS/MYOPATHY
(b) ACUTE RENAL FAILURE
(c) POSSIBLE DRUG RELATED HEPATIC DISORDERS