

February 06, 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 tablets
Amendment #0010 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 your letter of January 5, 2009 (copy attached) in which you provided comments on clinical pharmacology following the preliminary review of that section in the NDA. We have the following responses:

FDA Comment 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)

Kowa Response:

Kowa has long been aware of the FDA's concern about bioanalytical studies conducted by (b) (4) at the (b) (4) and (b) (4) sites in (b) (4). Kowa identified several studies conducted at the (b) (4)

facility for pitavastatin and elected to commission an independent audit which was conducted August 13-15, 2007 by^{(b)(4)} . It was concluded by^{(b)(4)} in their report: *"In summary, in our opinion, the Kowa method validation and analytical studies which we audited were satisfactorily conducted by^{(b)(4)} and the analytical data is valid and accurate. We found no reason to question the integrity or accuracy of the data reported."* A copy of the audit report is contained in this amendment as Appendix A to this cover letter. In addition we are submitting three additional analytical reports provided to us by^{(b)(4)} ; as a result of the audit.

FDA Comment B:

Pitavastatin is a 3R- and 5S- specific stereoisomer. You should provide data to demonstrate whether pitavastatin shows any chiral conversion via metabolism.

Kowa Response:

A full discussion in response to this comment is contained as Appendix B to this cover letter.

FDA Comment 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.

Kowa Response:

The plasma pitavastatin and pitavastatin lactone concentration data for study NK-104-1.37US are contained in transport files submitted 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: 5.807.00, created January 29, 2009

Sincerely yours,



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

APPENDIX A

**Audit Report – Bioanalytical Studies Performed at ^{(b) (4)} [REDACTED]
[REDACTED] August 13 – 15, 2007**

28 Page(s) has been Withheld in Full following this page as B4 (TS)

APPENDIX B

RESPONSE TO FDA COMMENT B

5 Page(s) has been Withheld in Full following this page as B4 (CCI/TS)

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-363 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Livalo
Established Name: pitavastatin (b) (4)
Strengths: 1 mg, 2 mg, 4 mg

Applicant: Kowa Company Ltd.
Agent for Applicant (if applicable): Kowa Research Institute Inc.

Date of Application: 10/1/08
Date of Receipt: 10/3/08
Date clock started after UN: N/A
Date of Filing Meeting: 12/1/08
Filing Date: 12/3/08
Action Goal Date (optional): User Fee Goal Date: 8/3/09

Indication(s) requested: patients with primary hyperlipidemia and mixed dyslipidemia as an adjunct to diet.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) X YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO X
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 60,492
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) 9/30/05 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 1/28/08 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 12/1/08

NDA #: 22-363

DRUG NAMES: Livalo (pitavastatin) Tablets

APPLICANT: Kowa Company Ltd.

BACKGROUND: Livalo is a statin drug that has been investigated under IND 60,492. The compound has been marketed in Japan since 2003.

ATTENDEES: Eric Colman, MD
Iffat Chowdhury, MD
Todd Sahlroot, PhD
Wei Liu, PhD
Karen Davis Bruno, PhD
Lee Elmore, PhD
Su Tran, PhD
Olen Stephens, PhD
Sally Choe, PhD
Johnny Lau, PhD
Susan Leibenhaut, MD

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	I. Chowdhury
Secondary Medical:	E. Colman
Statistical:	W. Liu
Pharmacology:	L. Elmore
Statistical Pharmacology:	TBD
Chemistry:	O. Stephens
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	J. Lau
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	S. Leibenhaut
OPS:	S. Tran
Regulatory Project Management:	K. Johnson
Other Consults:	N/A

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE