10/8/08

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-363

NDA ACKNOWLEDGMENT

Kowa Research Institute, Inc.
US Agent for Kowa Company Ltd.
Attention: Ross Laderman
Senior Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Pitavastatin Tablets 1 mg, 2 mg, and 4 mg.

Date of Application: October 1, 2008

Date of Receipt: October 3, 2008

Our Reference Number: NDA 22-363

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 2, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the

fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
10/8/2008 06:24:38 AM

KOWA

RESEARCH INSTITUTE, INC.

October 1, 2008

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
NK-104 (pitavastatin)
INITIAL NEW DRUG APPLICATION
PROPOSED TRADE NAME: LIVALO®

Dear Dr. Parks:

Kowa Company Limited (KCL) is pleased to submit an initial New Drug Application, NDA 22-363, for pitavastatin tablets (NK-104) with the proposed trade name, Livalo®. This product has been and is currently the subject of IND 60,492, held by Kowa Research Institute (KRI), a U.S. based KCL subsidiary.

DEVELOPMENT HISTORY:

Pitavastatin is a potent synthetic, competitive inhibitor of HMG-CoA reductase with preferential effects on the liver. A typical battery of efficacy pharmacology, safety pharmacology, pharmacokinetics, and toxicology studies was completed which KCL believes supports an appropriate risk to benefit profile across multiple species.

ADME and clinical pharmacology studies conducted indicate minimal metabolism by CYP liver enzymes and an essentially unchanged metabolic profile in the presence of clinically relevant concomitant medications with the exception of cyclosporin (4.6 fold in AUC_{0-t}), erythromycin (2.8 fold in AUC_{0-t}) and rifampicin (2.0 fold in C_{max}). Very modest increases were also seen in pitavastatin levels when co-administered with gemfibrozil (AUC increased 45%) and atazanavir (AUC increased 31%). The pharmacokinetic profile of NK-104 does not appear to significantly change (based on AUC) when given with or without food, in elderly versus young subjects or in Caucasians versus African Americans. In patients with mild or moderate liver cirrhosis, the AUC_{0-t} of pitavastatin increased 1.6-fold and 3.9-fold, respectively and the C_{max} increased 1.3-fold and 2.7-fold, respectively, compared to healthy subjects.

The safety, efficacy and pharmacokinetics of pitavastatin in pediatric populations have not been studied. A study in renal insufficiency patients showed a mild increase in

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

pitavastatin levels. The pharmacokinetic profile of NK-104 is consistent with once-a-day dosing for therapeutic effect.

Pitavastatin has been on the Japanese market since September 2003 when it was launched under the brand name Livalo®. It was also approved in Korea in January, 2005 and Thailand in November, 2007. It is currently pending approval in China.

The safety and efficacy data to support the proposed indication in this NDA originates from two primary sources:

1) The US and EU Phase 1 clinical pharmacology program and Phase 2 program (1 to 64 mg). Five clinical pharmacology studies which support the proposed US labeling were conducted in Asia.

2) The Phase 3 program (EU), including extension studies (1 to 4 mg).

The pitavastatin development program for the US NDA submission consists of a total of about 3,800 patients who have received the active drug or placebo. The Phase 2 US and EU program consists of approximately 1000 randomized patients treated for between 12 and 16 weeks with doses ranging from 1 to 64 mg. Based on the results of these studies, Kowa believes the clinical safety profile has been well defined for this period of treatment and the risks are not different from those of other approved compounds in the statin class. Kowa believes that the data support an adequate pitavastatin risk to benefit ratio in the dose range of 1 to 4 mg. Doses higher than 4 mg have been shown to have a less favorable benefit to risk ratio.

Following the Phase 2 studies, Kowa Research Europe (KRE), a separate arm of the Kowa Co. global organization, completed a series of nine Phase 3 safety and efficacy studies (five 12-week non inferiority studies + 4 extension studies) in Europe, Russia and India that constitute the primary efficacy and safety data base. (Although interim data from extension study NK-104-310 is included in this NDA the final results of the study were not used to assess safety or efficacy since the study itself was not completed by the time of the NDA submission).

The integrated core safety database for the NDA submission contains 5 Phase 2 studies, 5 Phase 3 core studies and 4 Phase 3 extension studies. It includes about 3,800 patients of which about 3,300 were given the active pitavastatin. The breakdown by dose is about 200 patients on 1 mg, 800 patients on 2 mg and 2,300 patients on 4 mg. About 350 patients in the pitavastatin 2 mg group and about 1300 patients in the pitavastatin 4mg group met long term exposure criteria of 52 weeks.

In addition to the core data, Japanese post-marketing surveillance data available in Japan since the launch of Livalo® in 2003 (1, 2 and 4 mg dose), as well as other Asian regional studies and formulation studies are summarized as supportive safety data in this NDA. Also the Japanese safety and efficacy data used to support the approval for marketing of Livalo® in Japan (1, 2 and 4 mg dose) is included in this NDA in the form of an English translation of the clinical summary of the Japanese NDA. The Japanese safety and efficacy database consists of 8 clinical pharmacology studies conducted in approximately 140 healthy subjects and 6 subjects with hepatic dysfunction. In addition, 8 safety and efficacy studies in approximately 1016 subjects with primary hypercholesterolemia or mixed dyslipidemia are included. Of this total about 210 subjects received pitavastatin for 1 year and 13 of 210 subjects received pitavastain for 2 years. A significant proportion of the patients in this program (519) were treated with a pitavastatin dose of 2 mg once daily. There were no deaths or reportable serious adverse events (SAEs) and the majority of the studies were conducted according to GCP principles.

Livalo® post-marketing surveillance data from Japan are currently available and more data are being collected on an ongoing basis. By the end of 2008, we estimate that the prescriptions written for Livalo® in Japan represent a total of over 800,000 patient years of exposure. Kowa believes that this database supports a significant reduction in the risks associated with post-approval, early marketing experiences in larger and more diverse patient populations.

An End-of-Phase 2 Meeting was held on September 20, 2005. The clinical findings and the non-clinical program were discussed along with the Phase 3 clinical plan to determine the adequacy of Kowa's development program to support the submission of this New Drug Application. Following the September 20, 2005 meeting a separate EOP 2 CMC meeting was scheduled but later cancelled by mutual agreement with the FDA as all questions were addressed adequately in advance through correspondence and phone contact with the Office of New Drug Chemistry.

Kowa believes that, based on the clinical data, the intended starting dose of pitavastatin is similar in its therapeutic performance to the most commonly prescribed dose of simvastatin and atorvastatin. It also exhibits a similar safety profile. An advantage of this compound is its simple metabolism. It is minimally metabolized via the CYP450 enzyme pathway, therefore it possesses a low risk of drug-drug interactions with the most common metabolic pathway. It has been determined that pitavastatin is a substrate of OATP2 (OATP1B1) and drugs which inhibit OATP2 increase plasma concentration of pitavastatin.

BACKGROUND AND REGULATORY HISTORY OF PITAVASTATIN:

In 1992, this compound was licensed from Nissan Chemical Co. (b) (4) [redacted] The product was developed by Kowa Co., Ltd (KCL) as 1 mg and 2 mg tablets and launched in Japan in 2003. The approved doses in Japan are 1 mg, 2 mg and 4 mg.

During Japanese development, Kowa sub-licensed NK-104 to Negma Laboratories for development in Europe and later to Sankyo US for development in the United States. Development in these regions was essentially independent of one another but the three companies engaged in routine communication. Novartis Pharmaceuticals later acquired Negma to obtain pitavastatin licensing rights in Europe.

Negma conducted its Phase 1 program with doses of 1 - 24 mg and Phase 2 program with doses of 1 – 8 mg. Sankyo followed another Phase I program with doses of 24mg to 64mg and conducted a Phase 2 study using 8, 16, 32, 64 mg. (b) (4) [redacted]

Novartis subsequently returned the rights to KCL in 2005 and Kowa Research Europe (KCL's European subsidiary) initiated a new Phase 3 program with 1, 2 and 4 mg doses.

Subsequently, the development rights to the product in the United States were returned to KCL from Sankyo. It was then that Kowa Research Institute (KRI), KCL's U.S. subsidiary, began development work by acquiring the IND previously held by Sankyo. The objective was to utilize the ongoing Phase 3 work in Europe to support the filing of an NDA in the U.S. An End-of-Phase 2 meeting was held, after KRI licensing acquisition, with the Division to discuss the Phase 3 program and outline requirements for the NDA.

REVIEW CONSIDERATIONS FOR THIS NDA:

As noted above and in section 1.12.11 portions of this NDA (in e-CTD format) are based on the CTD assembled by KCL's European office (KRE) for submission in Europe. Specifically, portions of Module 2, the nonclinical study reports in Module 4 and most of the clinical reports section of Module 5 have been extracted from the European CTD. Module 1, some portions of Module 2, the entirety of Module 3 and the ISS/ISE portions of Module 5 have been written by KCL.

KCL has elected, for the sake of completeness and continuity of data, to utilize most of the information in the European CTD which has then been incorporated into this NDA. However there are some significant points for the FDA to consider when reviewing this NDA:

1) (b) (4) [redacted]

2) The commercial manufacturer (Patheon) described in this NDA differs from that in Europe and we have conducted a specific bioequivalence study and dissolution comparability testing to support the use of drug product produced by Patheon.

3) As previously mentioned during the pre-NDA Meeting the final clinical study report for study NK-104-310 was not planned for inclusion in the NDA and is not included. Although an interim report from the EU CTD has been left intact (section 5.3.5.4) in Module 5 for completeness, we have not utilized data from this report to support any safety or efficacy conclusions about the drug.

Some documents in the eCTD, including portions of the ISS and Module 2.7 are comprised of cross-references to documents located elsewhere in the eCTD. These cross-references have been made using PDF-based hypertext-links in the eCTD. If a document is cross-referenced in this manner, it is noted within the referencing document.

The study reports in Module 5 are being submitted as legacy reports. These reports have the narrative portion (including the appendices) as a single monolithic file, unless the report is physically larger than that allowed by the guidance. Where applicable, CRFs, datasets, and data-definition-tables are being submitted as separate files.

Appended to this cover letter are four Annexes with information not elsewhere classified in the CTD hierarchy.

- Annex 1 contains a fact sheet as background for the proposed trade name, Livalo®, for this pitavastatin tablet.
- Annex 2 contains a summary table which identifies important IND correspondence between Kowa and the FDA. A copy of each piece of correspondence is included.
- Annex 3 contains a tabular listing of all IND submissions under IND 60,492 for the reviewers' reference if necessary.

- Annex 4 contains form FDA-3674, Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j)).

With regard to the production facilities for pitavastatin, (b) (4) the API and Patheon, Inc. for the drug product, these facilities are ready and prepared for inspection by the FDA.

This submission of NDA 22-363 consists of 2 DVDs, totaling approximately 9 -9.5 gigabytes. The submission is virus free. The following was used to check the files for viruses:

Trend Micro OfficeScan
Version 7.0
Virus Definitions: 5.569.00, created September 28, 2008

Should you have any questions, please do not hesitate to contact me at any time at (919) 433-1603.

Sincerely yours,

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

11/1/05

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,492

KOWA Research Institute Institute, Inc.
Attention: Ross Laderman
Senior Director, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Please refer to your Investigational New Drug Application (IND)submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NK-104 (pitavastatin) Tablets.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on September 20, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure