

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-363**

**CHEMISTRY REVIEW(S)**

7/20/09



Food and Drug Administration  
Silver Spring, MD 20993

**CMC Memo to File**

|          |                                |
|----------|--------------------------------|
| To:      | NDA                            |
| Date     | 20 JUL 2009                    |
| Sponsor: | Kowa                           |
| Drug:    | Livalo® (pitavastatin) tablets |
| Subject  | Approval recommendation        |
| Reviewer | Dr. Olen Stephens              |

Pursuant the overall "acceptable" recommendation given on 15-JUL-2009 of the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 22-363 be approved.

HFD-/Division File  
HFD-510  
HFD-510/K. Johnson

\_\_\_\_\_  
Olen Stephens, Ph.D.  
Chemistry Reviewer

\_\_\_\_\_  
Christine Moore, Ph.D.  
Acting Deputy Director, ONDQA

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/s/

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Olen Stephens  
7/20/2009 01:06:00 PM  
CHEMIST

Christine Moore  
7/20/2009 03:10:14 PM  
CHEMIST  
Division I Director (acting)  
Deputy (acting)  
ONDQA/CDER/FDA

7/14/09

**Livalo®  
(pitavastatin) tablet  
NDA 22-363**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Kowa Company Limited  
4-14 Nihonbashi-honcho 3-chome  
Chuo-ku  
Tokyo 103-8433 Japan

**Indication:** Pitavastatin is indicated as an adjunct to diet to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia.

**Presentation:** Pitavastatin drug product is an immediate-release, round biconvex, white film-coated tablets with formulations of 1 mg, 2 mg, and 4 mg pitavastatin free base per tablet, corresponding to 1.045 mg, 2.09 mg, and 4.18 mg pitavastatin calcium. The tablets are debossed with "KC" on one side and "1", "2" or "4" on the reverse side. The approximate dimensions for the coated tablets are:

- 1 mg - 6.5 mm diameter x 3.0 mm thick
- 2 mg - 8 mm diameter x 3.8 mm thick
- 4 mg- 10.5 mm diameter x 5.0 mm thick

The 1 mg, 2 mg, and 4 mg tablets are packaged in 90-count HDPE bottles with inductive-sealed (b) (4) child-resistant closures containing cotton and desiccant. Physician samples of the 2 mg and 4 mg tablets are packaged in coated (b) (4) aluminum foil blisters containing 7 tablets per card.

**EER Status:** Pending

**Consults:** EA – Categorical exclusion granted  
Methods Validation – Revalidation by Agency was not requested  
Biopharm – Acceptable, 14-Jul-09, H. Mahayni  
DMEPA – Pending labeling review

**Original Submission:** 03-Oct-2008

**Re-submissions:** N/A

**Post-Approval CMC Agreements:**

Beyond the typical stability commitments, the applicant was asked to provide written assurance regarding content uniformity testing and a commitment to revise the dissolution test method specification within one year of NDA approval.

**Drug Substance:**

Pitavastatin calcium, a new molecular entity, is monocalcium bis[(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoate]. Pitavastatin calcium is a white to pale yellow powder that is very slightly soluble in water over pH 2 to 12, and sparingly soluble in alcohols and highly soluble in ethylene glycol, pyridine and tetrahydrofuran. Pitavastatin has 2 chiral centers and multiple polymorphs are known. The drug substance manufacturing will be provided by (b) (4). Details of the manufacturing process are provided in associated DMFs, which have been fully reviewed. The specifications for the drug substance included tests and limits for identity (IR), appearance, chirality (b) (4) and microbial content.

**Conclusion:** The drug substance is acceptable.

**Drug Product:**

Livalo® tablets are available in 1 mg, 2 mg, and 4 mg strength film coated tablets. The different strengths are compositionally proportional and derived from a (b) (4) including: lactose monohydrate, HPMC, low-substituted hydroxypropyl cellulose, magnesium aluminometasilicate, and magnesium stearate. All excipients are compendial or composed of a mixture of compendial excipients (b) (4). The manufacturing process consists of (b) (4). The in-process controls include limits on (b) (4). Critical aspects for the manufacturing process include (b) (4).

The final product specification includes test and acceptance criteria for appearance, identification (HPLC, TLC), assay (HPLC), dosage uniformity, related substances (HPLC), stereoisomers (HPLC), dissolution, and microbial limits. The analytical procedures used are appropriately validated.

The expiration dating period grantable for the Livalo® (pitavastatin) tablets in 90-count HDPE bottles is 36 months with storage conditions of 25°C (77°F); excursions

permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature]; the expiration dating period grantable for the Livalo® (pitavastatin) tablets in 7-count blisters for physician samples is 24 months with the same storage conditions.

**Conclusion:** The drug product is satisfactory.

**Additional Items:**

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

**Overall Conclusion:** From a CMC perspective, the application is recommended for approval pending an Acceptable recommendation from Office of Compliance, and pending reviews from DMEPA on labeling.

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/s/

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Christine Moore  
7/14/2009 04:55:56 PM  
CHEMIST

**CMC Memo to File**

|          |                                  |
|----------|----------------------------------|
| Date     | 14 July 2009                     |
| NDA#     | 22-363                           |
|          | Phase 4 Agreement and EES Report |
| Sponsor: | Kowa Company Limited             |
| Drug:    | Livalo® (pitavastatin) tablet    |
| Reviewer | Dr. Olen Stephens                |

The following correspondence was sent to the applicant stemming from the ONDQA Biopharmaceutics review of the dissolution data. A Phase 4 agreement was requested; the applicant's response is included below:

*The FDA has made the following request of Kowa:*

*Based on the dissolution data provided on the clinical, stability and registration batches for each strength, a single-point dissolution test specification of NLT <sup>(b) (4)</sup> ( $Q = \sup{(b) (4)}$ ) in 30 minutes is recommended.*

*Please submit a Phase 4 agreement to revise the dissolution test method within one year of NDA approval to have a single point specification of NLT <sup>(b) (4)</sup> ( $Q = \sup{(b) (4)}$ ) in 30 minutes.*

**Kowa Agreement:**

**Within one year following approval of this NDA Kowa Company Limited agrees to develop and adopt a single point dissolution test method and specification of NLT <sup>(b) (4)</sup> ( $Q = \sup{(b) (4)}$ ) in 30 minutes.**

There are no other CMC deficiencies. From a CMC perspective, the application is recommended for approval pending an Acceptable recommendation from Office of Compliance, and pending reviews from OSE on labeling.

HFD-/Division File  
HFD-510  
HFD-510/K. Johnson

\_\_\_\_\_  
Olen Stephens, Ph.D.  
Chemistry Reviewer

\_\_\_\_\_  
Ali Al-Hakim, Ph.D.  
Branch II Chief, ONDQA

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/s/

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Olen Stephens  
7/14/2009 10:49:40 AM  
CHEMIST

Ali Al-Hakim  
7/14/2009 01:03:18 PM  
CHEMIST

5/11/09



**CHEMISTRY REVIEW**



**NDA 22-363**

**Livalo  
(pitavastatin calcium) tablet**

**Kowa Company**

**Olen M. Stephens**

**Review Chemist**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**



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# Chemistry Review Data Sheet

1. NDA or ANDA 22-363
2. REVIEW #: 2
3. REVIEW DATE: 7-MAY-2009
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

|                                                                                                               |             |
|---------------------------------------------------------------------------------------------------------------|-------------|
| Original Submission                                                                                           | 03-OCT-2008 |
| Amendment (BZ) (control of manufacturing process; container closure composition and certificates of analysis) | 21-NOV-2008 |

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

|                                                  |             |
|--------------------------------------------------|-------------|
| Amendment (BC) (response to information request) | 1-APR-2009  |
| Amendment (BC) (stability data)                  | 23-APR-2009 |

7. NAME & ADDRESS OF APPLICANT:

Name: Kowa Company Limited  
4-14 Nihonbashi-honcho 3-chome  
Address: Chuo-ku  
Tokyo 103-8433 Japan



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Kowa Research Institute, Inc.  
430 Davis Drive  
Representative: Suite 200  
Morrisville, NC 27560  
919-433-1600  
Telephone: 81(0)3 3279 7410

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Livalo (proposed)
- b) Non-Proprietary Name (USAN): Pitavastatin
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1 (new molecular entity)
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Pitavastatin is indicated as an adjunct to diet to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia.

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1, 2, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

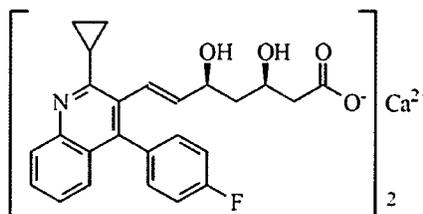
SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Monocalcium bis[(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoate]

 CAS registry number: 147526-32-7  
(NK-104)

 $C_{50}H_{46}CaF_2N_2O_8$ 

Molecular Weight: 880.98

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

| DMF #   | TYPE | HOLDER  | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS |
|---------|------|---------|-----------------|-------------------|---------------------|-----------------------|----------|
| (b) (4) |      | (b) (4) | Pitavastatin    | 1                 | Adequate            | 05-MAY-2009           | Type II  |
|         |      | (b) (4) |                 | 1                 | Adequate            | 10-FEB-2009           | Type IV  |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |
|         |      |         |                 | 4                 | N/A                 |                       | Type III |

<sup>1</sup> Action codes for DMF Table:



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| IND      | 60,492             |             |

### 18. STATUS:

#### ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE        | REVIEWER                        |
|-------------------------------|----------------|-------------|---------------------------------|
| Biometrics                    | Pending        |             | Wei Liu                         |
| EES                           | Pending        |             | Office of Compliance            |
| Pharm/Tox                     | Pending        |             | Calvin Elmore                   |
| Biopharm                      | Pending        |             | Johnny S. W. Lau; Houda Mahayni |
| LNC                           | Not Required   |             |                                 |
| Methods Validation            | Not Required   |             |                                 |
| OSE                           | Pending        |             | DMEPA and DDMAC                 |
| EA                            | Adequate       | 11-MAR-2009 | Olen Stephens                   |
| Microbiology                  | NA             |             |                                 |

**Patheon site scheduled to be inspected started 11-MAY-2009.**

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:

# The Chemistry Review for NDA 22-363

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an Acceptable recommendation from Office of Compliance.

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – Biowaiver for the 1 mg strength (b) (4) dissolution.
3. OSE – Labeling.

The expiration dating period grantable for the Livalo® (pitavastatin) tablets in 90-count HDPE bottles is 36 months with storage conditions of 25°C (77°F); excursions permitted to 15- 30°C (59-86°F) [see USP Controlled Room Temperature]; the expiration dating period grantable for the Livalo® (pitavastatin) tablets in 7-count blisters for physician samples is 24 months with the same storage conditions. This should be included in the action letter.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following are CMC agreements (i.e., these are NOT post-marketing commitments or requirements and will NOT be posted on FDA's website as per FDAAA):

(b) (4)



## Executive Summary Section

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

The USAN and INN name for the active pharmaceutical ingredient is pitavastatin, which is a new molecular entity. Detailed information regarding the drug substance characterization, manufacturing and controls was provided in DMF (b) (4) which has been reviewed and found adequate to support this application. The drug substance is produced as (b) (4) which is consistently manufactured by controlling (b) (4)

The particle size of the drug substance is a critical parameter that affects dissolution rate of the drug substance; the particle size is controlled at (b) (4) 1.

Pitavastatin's solubility is very slightly soluble in water (b) (4) (water), regardless of the pH's ranging from 2 to 12. Pitavastatin is highly soluble in organic solvents like tetrahydrofuran, pyridine, and ethylene glycol. The drug substance is minimally soluble in methanol and ethanol.

Stability data for pitavastatin was covered in DMF (b) (4). The review of DMF found this data adequate with an appropriately assigned retest period.

The drug product is an immediate release film-coated tablet containing pitavastatin calcium in three strengths: 1.045 mg, 2.09 mg, and 4.18 mg, which corresponds to 1 mg, 2 mg, and 4 mg of pitavastatin free base. Except for the color (b) (4) coating the tablets, all the excipients are pharmacopeial (USP/NF). Critical parameters in the manufacturing process were identified as: (b) (4)

The 1 mg, 2 mg, and 4 mg tablets are packaged in 90-count HDPE bottles; the 2 mg and 4 mg tablets are packaged in 7-count blisters for physician samples. The three dosage forms are derived from a common (b) (4) and are compositionally proportional. The applicant proposed an expiration date of 36 months for the 90-count HDPE bottles, which is supported by 36-months of real time stability data from supportive batches in packaging configurations and 15-months of stability data from primary batches. The expiration date for the 2-mg and 4-mg blister configurations is limited to 24-months because only a sub-set of the supportive blister configurations is similar to the commercial blister configuration, preventing all of the long-term supportive data from being bridged to the 12-months of primary stability data.



## CHEMISTRY REVIEW



### Executive Summary Section

#### **B. Description of How the Drug Product is Intended to be Used**

Pitavastatin tablets will be dispensed by prescription only for the management of hypelipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol. The recommended dose is 2 mg to 4 mg once daily at any time of the day with or without food. The 1 mg dose is available to the physician for discretionary use in patients that may benefit from a lower dose.

#### **C. Basis for Approvability or Not-Approval Recommendation**

Chemistry, Manufacturing and Controls deficiencies for the drug substance and the drug product were communicated to the applicant (11-MAR-2009) and have been sufficiently addressed.

The following recommendations are pending but will not have an impact on the specific findings discussed in this CMC review:

1. Office of Compliance – GMP status of the commercial manufacturing and testing facilities listed in the NDA.
2. ONDQA Biopharm Staff – Biowaiver for the 1 mg strength (b) (4) dissolution.
3. OSE – Labeling.

### **III. Administrative**

- A. Reviewer's Signature**      electronically signed in DFS  
Olen M. Stephens
- B. Endorsement Block**      electronically signed in DFS
- C. CC Block**      electronically signed in DFS

# 20 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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/s/

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Olen Stephens  
5/11/2009 10:05:10 AM  
CHEMIST  
CMC Review 2 with Labeling comments

Ali Al-Hakim  
5/11/2009 10:18:42 AM  
CHEMIST

3/11/09



**CHEMISTRY REVIEW**



**NDA 22-363**

**Livalo  
(pitavastatin calcium) tablet**

**Kowa Company**

**Olen M. Stephens**

**Review Chemist**

**Office of New Drug Quality Assessment  
Pre-Marketing Division I, Branch II  
for the  
Division of Metabolism and Endocrinology Products**



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# Chemistry Review Data Sheet

1. NDA or ANDA 22-363
2. REVIEW #: 1
3. REVIEW DATE: 25-FEB-2009
4. REVIEWER: Olen M. Stephens
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original Submission

03-OCT-2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

03-OCT-2008

Amendment (BZ) (control of manufacturing process; container closure composition and certificates of analysis)

21-NOV-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Kowa Company Limited

4-14 Nihonbashi-honcho 3-chome

Address: Chuo-ku

Tokyo 103-8433 Japan



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

Kowa Research Institute, Inc.  
430 Davis Drive  
Representative: Suite 200  
Morrisville, NC 27560  
919-433-1600  
Telephone: 81(0)3 3279 7410

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Livalo (proposed)
- b) Non-Proprietary Name (USAN): Pitavastatin
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1 (new molecular entity)
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Pitavastatin is indicated as an adjunct to diet to reduce total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides and to increase HDL-cholesterol in adult patients with primary hypercholesterolemia and mixed dyslipidemia.

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 1, 2, and 4 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

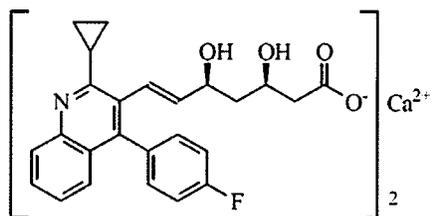
SPOTS product – Form Completed

Not a SPOTS product

## Chemistry Review Data Sheet

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Monocalcium bis[(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoate]

 CAS registry number: 147526-32-7  
(NK-104)

 $C_{50}H_{46}CaF_2N_2O_8$ 

Molecular Weight: 880.98

**17. RELATED/SUPPORTING DOCUMENTS:**
**A. DMFs:**

| DMF #   | TYPE    | HOLDER  | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS     |
|---------|---------|---------|-----------------|-------------------|---------------------|-----------------------|--------------|
| (b) (4) | (b) (4) | (b) (4) | Pitavastatin    | 7                 | Under Review        | 03-MAR-2009           | Under Review |
| (b) (4) | (b) (4) | (b) (4) |                 | 1                 | Adequate            | 10-FEB-2009           | Type IV      |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |
| (b) (4) | (b) (4) | (b) (4) |                 | 4                 | N/A                 |                       | Type III     |



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
| IND      | 60,492             |             |

### 18. STATUS:

#### ONDC:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE        | REVIEWER                        |
|-------------------------------|----------------|-------------|---------------------------------|
| Biometrics                    | Pending        |             | Wei Liu                         |
| EES                           | Pending        |             |                                 |
| Pharm/Tox                     | Pending        |             | Calvin Elmore                   |
| Biopharm                      | Pending        |             | Johnny S. W. Lau; Houda Mahayni |
| LNC                           |                |             |                                 |
| Methods Validation            | Not Required   |             |                                 |
| OPDRA                         |                |             |                                 |
| EA                            | Adequate       | 11-MAR-2009 | Olen Stephens                   |
| Microbiology                  | NA             |             |                                 |

### 19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. \_\_\_ Yes \_\_\_ No If no, explain reason(s) below:



# The Chemistry Review for NDA 22-363

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an "Acceptable" Office of Compliance recommendation.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

(b) (4)



### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

The USAN and INN name for the active pharmaceutical ingredient is pitavastatin, which is a new molecular entity. Detailed information regarding the drug substance characterization, manufacturing and controls was provided in DMF (b) (4), which has been reviewed and found adequate to support this application. The drug substance is produced as (b) (4) which is consistently manufactured by controlling (b) (4)

The particle size of the drug substance is a critical parameter that affects dissolution rate of the drug substance; the particle size is controlled at (b) (4)

Pitavastatin's solubility is very slightly soluble in water (b) (4) (water), regardless of the pH's ranging from 2 to 12. Pitavastatin is highly soluble in organic solvents like tetrahydrofuran, pyridine, and ethylene glycol. The drug substance is minimally soluble in methanol and ethanol.

Stability data for pitavastatin was covered in DMF (b) (4). The review of DMF found this data adequate with an appropriately assigned retest period.



Executive Summary Section

The drug product is an immediate release film-coated tablet containing pitavastatin in three strengths: 1.045 mg, 2.09 mg, and 4.18 mg, which corresponds to 1 mg, 2 mg, and 4 mg of pitavastatin free base. Except for the color <sup>(b) (4)</sup> coating the tablets, all the excipients are pharmacopeial (USP/NF). Critical parameters in the manufacturing process were identified as: <sup>(b) (4)</sup>

The 1 mg, 2 mg, and 4 mg tablets are packaged in 90-count HDPE bottles; the 2 mg and 4 mg tablets are packaged in 7-count blisters for physician samples. The three dosage forms are derived from a <sup>(b) (4)</sup> and are compositionally proportional. The proposed expiration date of 36 months is supported by real time stability data from supportive batches in similar packaging configurations for both the commercial packaging configurations. The expiration date will be established upon review of a comparison of the container closure configurations and materials used in the supportive and commercial configurations.

**B. Description of How the Drug Product is Intended to be Used**

Pitavastatin tablets will be dispensed by prescription only for the management of hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol. The recommended dose is 2 mg to 4 mg once daily at any time of the day with or without food. The 1 mg dose is available to the physician for discretionary use in patients that may benefit from a lower dose.

**C. Basis for Approvability or Not-Approval Recommendation**

Chemistry, Manufacturing and Controls deficiencies for the drug substance and the drug product will be communicated to the applicant (see CMC comments on page 73 of this review).

The facilities used in the manufacture and control of the drug substance and drug product have been submitted for evaluation to the Office of Compliance and are pending inspection.



**III. Administrative**

- A. Reviewer's Signature**      electronically signed in DFS  
Olen M. Stephens
- B. Endorsement Block**      electronically signed in DFS
- C. CC Block**      electronically signed in DFS

# 6 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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

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Olen Stephens  
3/11/2009 11:41:31 AM  
CHEMIST

Ali Al-Hakim  
3/11/2009 11:55:11 AM  
CHEMIST

12/1/08

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Division of Metabolism and Endocrinology Products**

**NDA:** 22-363

**Applicant:** Kowa Company

**Stamp Date:** 03-OCT-2008

**PDUFA Date:** 03-AUG-2009

**Proposed Proprietary Name:** Livalo

**Established Name:** Pitavastatin

**Dosage form and strength:** Immediate release tablet –  
1, 2, and 4 mg (free base)

**Route of Administration:** oral

**Indications:** To reduce total cholesterol, LDL-cholesterol,  
apolipoprotein B, and triglycerides, and to increase  
HDL-cholesterol

**PAL:** Su (Suong) Tran, Branch II/DPA I/ONDQA

**ONDQA Fileability:** Yes

**Comments for 74-Day Letter:** Yes, on the last page.

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

| CONSULTS/ CMC RELATED REVIEWS | COMMENT                                                                                                 |
|-------------------------------|---------------------------------------------------------------------------------------------------------|
| Biopharmaceutics              | A consult review of the biowaiver request will be requested of the ONDQA Biopharmaceutics Review Staff. |
| CDRH or CBER                  | <i>Not Applicable</i>                                                                                   |
| EA                            | Categorical exclusion request will be assessed by Primary Reviewer.                                     |
| EES                           | EER was sent to Office of Compliance on 08-OCT-2008.                                                    |
| OSE                           | <i>Labeling consult request will be sent as part of DMEP's request.</i>                                 |
| Methods Validation            | <i>Validation may be requested of FDA labs after test methods are finalized.</i>                        |
| Microbiology                  | <i>Not Applicable</i>                                                                                   |
| Pharm/Tox                     | Review of safety limits on impurities.                                                                  |

**Summary: [See the discussion in Critical Issues later in this review.]**

This is an electronic NDA, filed as a 505(b)(1) application for pitavastatin calcium, which is a New Molecular Entity. The product is a single-entity, immediate-release tablet available in the strengths of 1, 2, and 4 mg (free base) pitavastatin.

**Maximum daily dose is 4 mg (free base) pitavastatin.**

|                                |                                                                                                                                                                                |
|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Route of administration</b> | Oral                                                                                                                                                                           |
| <b>Dosage form</b>             | Immediate release tablet                                                                                                                                                       |
| <b>Package type</b>            | For commercial distribution: HDPE bottle with child-resistant closure and desiccant in 90-count (60 cc bottle) <sup>(b) (4)</sup><br>For physicians' samples: 7-count blisters |
| <b>Potency</b>                 | 1, 2, and 4 mg (free base) pitavastatin                                                                                                                                        |
| <b>Color</b>                   | White                                                                                                                                                                          |
| <b>Shape</b>                   | Round                                                                                                                                                                          |
| <b>Coating</b>                 | Film coated                                                                                                                                                                    |
| <b>Size</b>                    | [unknown] <i>Comment for the 74-day letter.</i>                                                                                                                                |
| <b>Scoring</b>                 | None                                                                                                                                                                           |
| <b>Imprint codes</b>           | Debossed "KC" on one side and "1", "2", or "4" on the other side                                                                                                               |
| <b>Symbols</b>                 | None                                                                                                                                                                           |

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**Drug substance:**

**[See the discussion in Critical Issues later in this review.]**

Reference is made to DMF (b) (4) for all CMC information on the drug substance pitavastatin calcium. The information available in the NDA is copied below and on the next pages.

The applicant claims that pitavastatin is a BCS Class I compound (Justification of Dissolution in section 3.2.P.5.6).

Pitavastatin calcium (NK-104) is a synthetic HMG-Co-A reductase inhibitor or statin indicated in the treatment of hypercholesterolemia and dyslipidaemia.

INN: pitavastatin

Chemical name: (+)-monocalcium *bis*{(3*R*, 5*S*, 6*E*)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}

Company name: pitavastatin or pitavastatin calcium

Laboratory codes: NK-104, NKS104 or NKS-104A

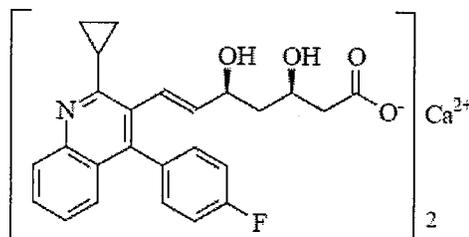
JAN: pitavastatin calcium

CAS registry number: 147526-32-7

Further information pertaining to pitavastatin may be found in DMF (b) (4) controlled by (b) (4)

**2.3.S.1.2 Structure**

The absolute stereochemical structure of pitavastatin calcium is provided below:



**Figure 2.3.S.1.2-1 Structure of pitavastatin calcium**

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

Molecular weight: 880.98

# 21 Page(s) Withheld

X Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

Initial Quality Assessment  
Pre-Marketing Assessment Division 1 Branch 2

**CHEMISTRY NDA FILING CHECKLIST**

**IS THE CMC SECTION OF APPLICATION FILEABLE? Yes**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

|    | Content Parameter                                                                                                                          | Yes | No | Comment                                                       |
|----|--------------------------------------------------------------------------------------------------------------------------------------------|-----|----|---------------------------------------------------------------|
| 1  | Is the section legible, organized, indexed, and paginated adequately?                                                                      | x   |    |                                                               |
| 2  | Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)? | x   |    |                                                               |
| 3  | Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?  |     | x  | Request for this statement will be part of the 74-day letter. |
| 4  | Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?                                               | x   |    |                                                               |
| 5  | Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?                                                       | x   |    |                                                               |
| 6  | Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?                                                        | x   |    |                                                               |
| 7  | If applicable, has all information requested during the IND phases and at the pre-NDA meetings been included?                              | x   |    |                                                               |
| 8  | Have draft container labels and package insert been provided?                                                                              | x   |    |                                                               |
| 9  | Have all DMF References been identified?                                                                                                   | x   |    |                                                               |
| 10 | Is information on the investigational formulations included?                                                                               | x   |    |                                                               |
| 11 | Is information on the methods validation included?                                                                                         | x   |    |                                                               |
| 12 | If applicable, is documentation on the sterilization process validation included?                                                          |     |    | Not applicable: oral dosage form.                             |

**74-Day Letter – Comments to the Applicant:**

1. Because the dosage strengths are based on the free base pitavastatin, the established name of your product is “pitavastin”. Revise all labeling, where applicable, to replace (b) (4) with the correct established name “pitavastin”.
2. Confirm that the manufacturing and testing facilities listed in the NDA Form 356h are all the facilities involved in the manufacture and testing of the commercial drug substance and drug product and indicate whether each facility is ready for inspection or, if not, when it will be ready.
3. Provide the physical dimension of the finished tablet.
4. Provide a justification for the omission of blend (b) (4)
5. Provide references to the 21 CFR food additive regulations for the drug-contact components of the container closure systems used to package the drug substance and drug product.

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

-----  
Suong Tran  
12/1/2008 02:03:12 PM  
CHEMIST

as we discussed

Ali Al-Hakim  
12/1/2008 05:28:07 PM  
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

|                 |                       |                |                |
|-----------------|-----------------------|----------------|----------------|
| Application:    | NDA 22363/000         | Action Goal:   |                |
| Stamp:          | 03-OCT-2008           | District Goal: | 04-JUN-2009    |
| Regulatory Due: | 03-AUG-2009           | Brand Name:    | LIVALO TABLETS |
| Applicant:      | KOWA                  | Estab. Name:   |                |
|                 | 430 DAVIS DR STE 200  | Generic Name:  | PITAVASTATIN   |
|                 | MORRISVILLE, NC 27560 |                |                |
| Priority:       | 1S                    | Dosage Form:   | (TABLET)       |
| Org Code:       | 510                   | Strength:      | 1,2,4 MG       |

Application Comment:

Contacts: K. JOHNSON 301-796-1234 , Project Manager  
S. TRAN 301-796-1764 , Team Leader

-----  
Overall Recommendation: ACCEPTABLE on 15-JUL-2009 by E. JOHNSON (HFD-320) 301-796-3334  
-----

Establishment: CFN (b) (4) FEI (b) (4)  
(b) (4)  
(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Es... Comment: FULL ADDRESS:

(b) (4)  
(b) (4)

## ESTABLISHMENT EVALUATION REQUEST

## DETAIL REPORT

File: TCM OAI Status: NONE

| EMilestone Name       | Date        | Type | Insp. Date  | Decision & Reason | Creator |
|-----------------------|-------------|------|-------------|-------------------|---------|
| SUBMITTED TO OC       | 08-OCT-2008 |      |             |                   | TRANS   |
| SUBMITTED TO DO       | 08-OCT-2008 | PS   |             |                   | ADAMSS  |
| ASSIGNED INSPECTION T | 07-NOV-2008 | PS   |             |                   | KCULVER |
| INSPECTION SCHEDULED  | 25-MAR-2009 |      |             |                   | KCULVER |
| INSPECTION PERFORMED  | 15-MAY-2009 |      | 15-MAY-2009 |                   | KCULVER |

NO 483 ISSUED... PROCESS VALIDATION CAN BE REVIEWED IN ROUTINE GMP INSPECTION AT CSO'S DISCRETION.

|                   |             |  |  |                          |         |
|-------------------|-------------|--|--|--------------------------|---------|
| DO RECOMMENDATION | 01-JUN-2009 |  |  | ACCEPTABLE<br>INSPECTION | KCULVER |
|-------------------|-------------|--|--|--------------------------|---------|

N 483. PROCESS VALIDATION CAN BE REVIEWED IN ROUTINE GMP INSPECTION AT CSO'S DISCRETION.

|                |             |  |  |                                       |           |
|----------------|-------------|--|--|---------------------------------------|-----------|
| RECOMMENDATION | 01-JUN-2009 |  |  | ACCEPTABLE<br>DISTRICT RECOMMENDATION | FERGUSONS |
|----------------|-------------|--|--|---------------------------------------|-----------|

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Application:** NDA 22363/000

**Action Goal:**

**Submission Date:** 03-OCT-2008

**District Goal:** 04-JUN-2009

**Submission Priority:** 03-AUG-2009

**Applicant:** KOWA  
430 DAVIS DR STE 200  
MORRISVILLE, NC 27560

**Brand Name:** LIVALO TABLETS

**Estab. Name:**

**Generic Name:** PITAVASTATIN

**Dosage Form:** (TABLET)

**Priority:** 1S

**Strength:** 1,2,4 MG

**Org. Code:** 510

**Application Comment:**

|                      |            |                 |              |
|----------------------|------------|-----------------|--------------|
| <b>FDA Contacts:</b> | K. JOHNSON | Project Manager | 301-796-1234 |
|                      | S. TRAN    | Team Leader     | 301-796-1764 |

---

**Overall Recommendation:** ACCEPTABLE      on 15-JUL-2009      by E. JOHNSON      (HFD-320)      301-796-3334

---

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: (b) (4) FEI: (b) (4)  
 (b) (4)  
 (b) (4)  
**DMR No:** (b) (4) AADA:  
**Responsibilities:** DRUG SUBSTANCE MANUFACTURER  
**Estab. Comment:** FULL ADDRESS:  
 (b) (4)  
**Profile:** (b) (4) OAI Status: NONE

| <u>Milestone Name</u>     | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u>                       | <u>Creator</u> |
|---------------------------|-----------------------|---------------------|---------------------------|---------------------------------------|----------------|
| <u>Comment</u>            |                       |                     |                           | <u>Reason</u>                         |                |
| SUBMITTED TO OC           | 08-OCT-2008           |                     |                           |                                       | TRANS          |
| SUBMITTED TO DO           | 08-OCT-2008           | Product Specific    |                           |                                       | ADAMSS         |
| ASSIGNED INSPECTION TO IB | 16-NOV-2008           | Product Specific    |                           |                                       | ADAMSS         |
| INSPECTION SCHEDULED      | 05-MAY-2009           |                     | 25-JUN-2009               |                                       | IRIVERA        |
| DO RECOMMENDATION         | 15-JUL-2009           |                     |                           | ACCEPTABLE<br>INSPECTION              | JOHNSONE       |
| OC RECOMMENDATION         | 15-JUL-2009           |                     |                           | ACCEPTABLE<br>DISTRICT RECOMMENDATION | JOHNSONE       |

**FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT**

**Establishment:** CFN: 1510437 FEI: 1510437  
PATHEON PHARMACEUTICALS INC

2110 E GALBRAITH RD  
CINCINNATI, OH 452371625

**DMF No:** **AADA:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Estab. Comment:**

**Profile:** TABLETS, PROMPT RELEASE **OAI Status:** NONE

| <u>Milestone Name</u>                                                                              | <u>Milestone Date</u> | <u>Request Type</u> | <u>Planned Completion</u> | <u>Decision</u>         | <u>Creator</u> |
|----------------------------------------------------------------------------------------------------|-----------------------|---------------------|---------------------------|-------------------------|----------------|
| <u>Comment</u>                                                                                     |                       |                     |                           | <u>Reason</u>           |                |
| SUBMITTED TO OC                                                                                    | 08-OCT-2008           |                     |                           |                         | TRANS          |
| SUBMITTED TO DO                                                                                    | 08-OCT-2008           | Product Specific    |                           |                         | ADAMSS         |
| ASSIGNED INSPECTION TO IB                                                                          | 07-NOV-2008           | Product Specific    |                           |                         | KCULVER        |
| INSPECTION SCHEDULED                                                                               | 25-MAR-2009           |                     |                           |                         | KCULVER        |
| INSPECTION PERFORMED                                                                               | 15-MAY-2009           |                     | 15-MAY-2009               |                         | KCULVER        |
| NO 483 ISSUED... PROCESS VALIDATION CAN BE REVIEWED IN ROUTINE GMP INSPECTION AT CSO'S DISCRETION. |                       |                     |                           |                         |                |
| DO RECOMMENDATION                                                                                  | 01-JUN-2009           |                     |                           | ACCEPTABLE              | KCULVER        |
| NO 483. PROCESS VALIDATION CAN BE REVIEWED IN ROUTINE GMP INSPECTION AT O'S DISCRETION.            |                       |                     |                           | INSPECTION              |                |
| OC RECOMMENDATION                                                                                  | 01-JUN-2009           |                     |                           | ACCEPTABLE              | FERGUSONS      |
|                                                                                                    |                       |                     |                           | DISTRICT RECOMMENDATION |                |