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RESEARCH**

*APPLICATION NUMBER:*

**209875Orig1s000**

**SUMMARY REVIEW**

**Medical Officer 505(b)(2) NDA Review  
Division of Metabolism and Endocrine Products**

**NDA- 209875**

**Name of Drug/ Drug Substance-** pitavastatin sodium

**Sponsor-** Lupin Limited

**Date of Submission-** October 21, 2016

**PDUFA Goal Date-** August 21, 2017

**Medical Reviewer-** Iffat Nasrin Chowdhury, MD

**Deputy Division Director-** James P. Smith, MD, MS

**Executive Summary**

Lupin Limited submitted this NDA under Section 505(b)(2) for its pitavastatin tablet formulation in doses of 1, 2, and 4 mg. It contains a different salt, sodium salt, as compared to the listed drug, Livalo, which contains calcium salt. Lupin requests that the Agency's finding of efficacy and safety for Livalo be referenced for approval of its product. Livalo, or pitavastatin calcium, first approved in 2009, is a statin indicated for the treatment of primary hypercholesterolemia or mixed dyslipidemia.

The proposed indication for pitavastatin sodium is identical to that currently approved for Livalo:

Pitavastatin is a HMG-CoA reductase inhibitor indicated for:

- Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and to increase high-density lipoprotein cholesterol (HDL-C).

The applicant also proposes 1, 2, and 4 mg dosage formulations of pitavastatin sodium similar to the 1, 2, and 4 mg doses of Livalo currently available.

Two bioequivalence studies in fasted and fed conditions comparing the 4 mg doses of the two products were submitted to support the approval of pitavastatin sodium. These bioequivalence studies were reviewed in detail by Dr. Lei He from the Office of Clinical Pharmacology. The clinical pharmacology team found the Applicant's pitavastatin sodium to be bioequivalent to the listed drug, pitavastatin calcium, where the 90% confidence interval for pharmacokinetic parameters was within the acceptable range of 80-125%. Therefore, the clinical pharmacology team recommends approval of this product.

The biowaiver request for the lower strengths (1 and 2 mg) of pitavastatin sodium was submitted along with in vitro dissolution data to support the request. Following review of

in vitro dissolution data by the biopharmaceuticals reviewer, Dr. Hansong Chen, the biowaiver request was granted.

Dr. Parvaneh Espandiari and the pharmacology/toxicology (P/T) team reviewed the 28-day nonclinical bridging study. According to P/T review, the 28-day repeat-dose toxicity study was conducted with the proposed 505b2 product, pitavastatin sodium, and an unmarketed, uncharacterized pitavastatin calcium drug substance. Both formulations tested were manufactured by the Applicant (i.e., the pitavastatin calcium utilized was of unknown similarity to the listed drug). Therefore, the P/T team considered the 28-day toxicity study to be of limited value. However, according to the P/T team, toxicities observed with the Applicant's pitavastatin sodium formulation were typical of those generally known to occur in rodents with other statin drugs. P/T concluded that no other useful information could be derived from this study.

This deficiency was not considered by P/T enough to recommend against approval of pitavastatin sodium. Instead, P/T recommends the scientific bridge to the listed drug be relied on CMC data and the clinical bridging data, which was conducted with the listed drug.

The clinical team reviewed the safety data, including adverse event and laboratory data, from the two bioequivalence studies and found no clinically meaningful safety signals with administration of pitavastatin sodium when compared to pitavastatin calcium.

Since the clinical pharmacology team found bioequivalence between pitavastatin sodium and the listed drug pitavastatin calcium and considering that CMC found no deficiencies with pitavastatin sodium drug substance/ product and CMC considers the data submitted to CMC sufficient for bridging to the listed drug, the clinical team concludes a scientific bridge is established between the Applicant's pitavastatin sodium and the listed drug pitavastatin calcium using the two bioequivalence studies and the physiochemical data submitted to CMC. Therefore, the Agency's prior finding of efficacy and safety for Livalo can be referenced for approval for pitavastatin sodium.

On the basis of a sufficient bridge to pitavastatin's clinical and safety data and supported by the efficacy and safety data from the two bioequivalence studies, this reviewer recommends approval of this 505(b)(2) application for pitavastatin sodium. Labeling should reflect the approved pitavastatin calcium, Livalo.

## **Regulatory**

There were no previous meetings (e.g., pre-NDA or IND) between DMEP and Lupin Limited to discuss the requirements for development and approval of pitavastatin sodium tablets.

During the filing review for pitavastatin sodium, the non-clinical team identified that the company manufactured pitavastatin calcium at their own manufacturing facility to use in their 28-day bridging rat study comparing the toxicity of pitavastatin calcium and

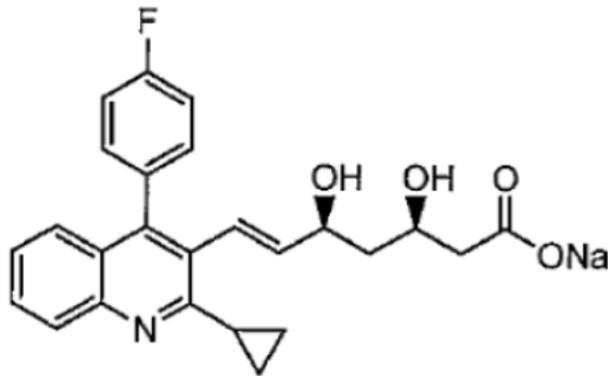
pitavastatin sodium. In order to bridge the impurity profile of the proposed drug to that of the listed drug Livalo, the bridging toxicity study should have included Livalo as the comparator instead of pitavastatin calcium produced in-house. This deficiency was listed in the the 74-day letter to the company, which stated that it would be a review issue whether clinical, CMC and other nonclinical data would be sufficient to establish an acceptable scientific bridge.

### Drug in Study

The CMC team review team, Dr. Xavier Ysern (drug substance) and Dr. Elise Luong (drug product) reviewed their respective parts of the CMC package. Please see their reviews for detailed CMC analysis.

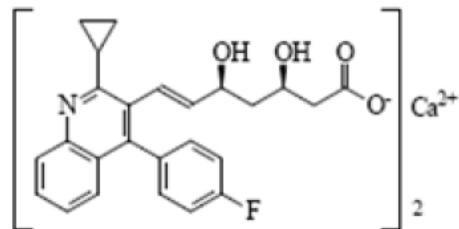
The chemical name of the drug substance of pitavastatin sodium is sodium (3R, 5S, E)-7-(2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl)-3,5-dihydroxyhept-6-enoate. The molecular formula is  $C_{25}H_{23}FNO_4Na$ . The chemical structure of pitavastatin sodium is depicted below.

**Figure 1: Chemical Structure of Pitavastatin Sodium**



Source: Pitavastatin Sodium NDA

For comparison, the chemical structure and molecular formula of pitavastatin calcium (Livalo) are shown below:



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

Molecular weight: 880.98

Source: Pitavastatin calcium NDA

The drug product for pitavastatin sodium is described as white to off-white, round, film-coated tablets. The following table summarizes the quantitative and qualitative composition of the drug product of pitavastatin sodium.

**Table 1: Drug Product Composition, Pitavastatin Sodium**

Ingredients	1 mg	2 mg	4 mg	% w/w	Category	Reference to Standards
	Quantity mg/tablet	Quantity mg/tablet	Quantity mg/tablet			
<b>CORE COMPOSITION</b>						
Pitavastatin sodium* (Equivalent to Pitavastatin)	1.052 (1.000)	2.103 (2.000)	4.206 (4.000)	1.276	Active	IH
Lactose monohydrate** (b) (4)	(b) (4)				(b) (4)	NF
Low Substituted Hydroxypropyl Cellulose (b) (4)	(b) (4)				(b) (4)	NF
Hypromellose (b) (4)	(b) (4)				(b) (4)	USP
Sodium bicarbonate (b) (4)	(b) (4)				(b) (4)	USP
(b) (4)	(b) (4)				(b) (4)	USP
(b) (4)	(b) (4)				(b) (4)	USP
(b) (4)	(b) (4)				(b) (4)	(b) (4)
Low Substituted Hydroxypropyl Cellulose (b) (4)	(b) (4)				(b) (4)	NF
Magnesium Stearate (b) (4)	(b) (4)				(b) (4)	NF
(b) (4)	(b) (4)				(b) (4)	--
(b) (4)	(b) (4)				(b) (4)	IH
(b) (4)	(b) (4)				(b) (4)	USP
<b>Total Weight of Coated Tablet (mg)</b>	<b>82.400</b>	<b>164.800</b>	<b>329.600</b>	<b>100.00</b>		--

q.s: quantity sufficient

For comparison, drug product composition for pitavastatin calcium is shown below:

**Table 2: Drug Product Composition, Pitavastatin calcium**

Table 2.3.P.1-1 Target Composition of the 1 mg, 2 mg, and 4 mg Pitavastatin Tablets

Component	Reference	Function	Quantity		
			1 mg Tablet (mg)	2 mg Tablet (mg)	4 mg Tablet (mg)
Pitavastatin Calcium	DMF	(b) (4)	1.045 <sup>1</sup>	2.09 <sup>1</sup>	4.18 <sup>1</sup>
Lactose Monohydrate	DMF	(b) (4)			
Low Substituted Hydroxypropyl Cellulose		(b) (4)			
Hypromellose		(b) (4)			
Magnesium Aluminometasilicate		(b) (4)			
Magnesium Stearate		(b) (4)			
<b>Total</b>			<b>80.00</b>	<b>160.00</b>	<b>320.00</b>
<b>Total</b>			<b>83.00</b>	<b>165.00</b>	<b>329.00</b>

<sup>1</sup> Equivalent to 1.00 mg, 2.00 mg and 4.00 mg of pitavastatin.

Source: Table from S-013 CMC supplement Quality review 9/2014.

*Reviewer Comment: The drug product pitavastatin sodium is similar to the listed drug pitavastatin calcium with the exception that pitavastatin sodium contains approximately (b) (4) of sodium bicarbonate. For comparison, there is approximately 106.5 mg of sodium bicarbonate and 250 mg of sodium alginate in one tablet of Gaviscon tablet.<sup>1</sup>*

**Biopharmaceutical Studies Submitted to NDA 209875**

The applicant submitted two bioequivalence studies, one in fasted condition and one in fed condition, to support the approval of pitavastatin sodium. Please see the review from Dr. He for complete clinical pharmacology analysis.

The following table summarizes the two bioequivalence studies conducted by the company:

**Table 3: Biopharmaceutical Trials with Pitavastatin sodium**

Type of Study/ Study Identifier	Objectives of Study	Study Design and Type of Control	Study Drug	Number of Subjects
<b>Bioequivalence Study/ LBC/ARL/16/056</b>	Primary objective was to demonstrate the bioequivalence between Test Product (T): Pitavastatin Tablets 4 mg and Reference Product (R): Livalo (Pitavastatin) Tablets 4 mg in normal, healthy, adult male and female human subjects, under <b>fasting</b> conditions.	Open label, two treatment, two period, two sequence, single dose crossover study design	Test Product: Pitavastatin sodium 4 mg  Reference Product: Livalo (Pitavastatin calcium)	36 subjects enrolled in the study  35 subjects considered for bioequivalence

<sup>1</sup> <https://www.medicines.org.uk/eme/medicine/20053>

Type of Study/ Study Identifier	Objectives of Study	Study Design and Type of Control	Study Drug	Number of Subjects
<b>Bioequivalence Study/ LBC/ARL/16/057</b>	Primary objective was to demonstrate the bioequivalence between Test Product (T): Pitavastatin Tablets 4 mg and Reference Product (R): Livalo® (Pitavastatin) Tablets 4 mg in normal, healthy, adult, male and female human subjects, under <b>fed</b> conditions.	Open label, two treatment, two period, two sequence, single dose, crossover study	105 mg	36 subjects enrolled in the study  32 subjects considered for bioequivalence

### Bioequivalence

#### Study LBC/ARL/16/056 (Fasting)

This was a randomized, open-label, single dose, cross-over study of pitavastatin sodium (Test) and pitavastatin calcium (Reference) in healthy adult male and female subjects under fasting conditions. Blood samples were drawn from pre-dose (collected within 1 hour prior to dosing) and up to 48 hours post dose in each study period. Analysis of plasma concentrations of study drug was done by a validated LC-MS/MS analytical method. The following table is from Dr. He's clinical pharmacology review.

**Table 4: Study LBC/ARL/16/056 (Fasting): Geometric Means, Ratios and 90% Confidence Intervals for Pitavastatin sodium (T) and Pitavastatin calcium (R) N=35**

Parameters	Geometric Mean		% GMR (T/R)	90% CI of GMR
	Test (T)	Reference (R)		
C <sub>max</sub> (ng/mL)	131.4	127.8	102.8	(95.7, 110.3)
AUC <sub>0-t</sub> (h*ng/mL)	294.06	280.06	105.0	(100.7, 109.5)
AUC <sub>0-inf</sub> (h*ng/mL)	319.08	305.39	104.5	(100.4, 108.7)

Source: Dr. He's clinical pharmacology review for NDA 209875

According to Dr. He's review, the results from Study LBC/ARL/16/056 (fasting study) demonstrate that Lupin's 4 mg pitavastatin sodium tablets (single administration) are bioequivalent to Kowa's Livalo 4 mg tablets (single administration). The geometric mean ratios of AUC<sub>inf</sub>, AUC<sub>0-t</sub> and C<sub>max</sub>, and the 90% confidence intervals for these ratios meet the bioequivalence criteria (Table 4). Therefore, pitavastatin sodium is bioequivalent to pitavastatin calcium.

### *Safety*

No serious adverse event was reported and one subject discontinued from treatment during administration of Reference product due to an adverse event of vomiting with mild burning pain in epigastrium. The reported adverse event was moderate in severity, possibly related to the study medication and resolved.

Review of individual subject laboratory data did not show any clinically meaningful safety signals (e.g., liver transaminase elevations greater than 3XULN, elevations in creatinine kinase) with single dose administration of Test and/or Reference product.

Study LBC/ARL/16/057 (Fed)

This was a randomized, open-label, single dose, cross-over study of pitavastatin sodium (Test) and pitavastatin calcium (Reference) in healthy adult male and female subjects under fed conditions. Blood samples were drawn from pre-dose (collected within 1 hour prior to dosing) and up to 48 hours post dose in each study period. Analysis of plasma concentrations of study drug was done by a validated LC-MS/MS analytical method. The following table is from Dr. He’s clinical pharmacology review.

**Table 5: Study LBC/ARL/16/057 (Fed): Geometric Means, Ratios and 90% Confidence Intervals for Pitavastatin sodium (T) and Pitavastatin calcium (R) (N=32)**

Parameters	Geometric Mean		% GMR (T/R)	90% CI of GMR
	Test (T)	Reference (R)		
Cmax (ng/mL)	74.5	80.5	92.5	(85.1, 100.8)
AUC0-t (h*ng/mL)	248.9	244.2	101.9	(96.4, 107.7)
AUC0-inf (h*ng/mL)	271.9	269.3	101.0	(95.9, 106.3)

Source: Dr. He’s clinical pharmacology review for NDA 209875

According to the clinical pharmacology review, the geometric mean ratios AUC0-inf, AUC0-t, and Cmax, and the 90% confidence interval for pitavastatin sodium fall wholly within 80-125% of the reference product.

After a high fat, high calorie breakfast, both the rate of absorption (Cmax) and the extent of absorption decreased for both pitavastatin sodium and pitavastatin calcium. There was approximately 40% decrease in Cmax and <20% decrease in AUC after high-fat food intake with both products. This effect is of no clinical significance and probably reflects a small delay in gastric emptying due to the presence of food.

*Safety*

Of the 36 subjects enrolled in the fed study, 32 subjected completed the entire duration; three subjects discontinued due to adverse events and 1 subject discontinued due to personal reasons.

Three adverse events (skin rash, diarrhea, and nausea with vomiting) were reported in Study ARL/16/057 in three subjects. The skin rash and diarrhea events occurred with pitavastatin sodium and were moderate in severity, probably related to study medication, and resolved. The nausea with vomiting occurred with Livalo and was moderate in severity, probably related to study medication, and resolved. No serious adverse event was reported during the course of the study.

Review of individual subject laboratory data did not show any clinically meaningful safety signals (e.g., liver transaminase elevations greater than 3XULN, elevations in creatinine kinase) with single dose administration of pitavastatin sodium and/or Livalo.

### *Drug-Drug Interaction*

The sponsor proposes to label pitavastatin sodium with the same drug interactions as in the Livalo label (cyclosporine, erythromycin, rifampin, gemfibrozil, other fibrates, niacin, colchicine and warfarin) without conducting separate DDI studies for its product. The clinical pharmacology team agreed with the sponsor that DDI studies were not needed for pitavastatin sodium as the active moiety (pitavastatin) is the same for pitavastatin sodium and Livalo.

### **AUDITS**

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection because OSIS recently inspected the analytical and clinical facilities for the bioequivalence trials.

### **CMC**

According to Dr. Ysem, the drug substance pitavastatin sodium is a synthetic small molecule. Pitavastatin, the active moiety, inhibits the liver enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase). The drug substance is stored (b) (4). The CMC information of the drug substance Pitavastatin Sodium is referred to DMF (b) (4). DMF (b) (4) is currently active and deemed acceptable (CMC Review, dated 30-Mar-2017). As stated in the CMC review, Lupin Pharmaceuticals is both the Applicant under NDA 209875 and the Holder of the DMF (b) (4).

According to Dr. Ysem, the quality of the described drug substance is deemed acceptable to support its use in the manufacture of the proposed drug product pitavastatin tablet.

The drug product is an immediate release oral tablet. Dosage strengths are 1 mg, 2 mg, and 4 mg pitavastatin, which are equivalent to 1.052 mg, 2.103 mg, and 4.206 mg pitavastatin sodium, respectively. According to Dr. Luong, the regulatory drug product specification is adequate based on the supporting release and stability data and ICH guidelines for this type of dosage form. Limits on degradants meet the applicable ICH identification and qualification threshold for the maximum daily dose of 4 mg. They are the same as impurities listed in the drug substance specification (with the exception of (b) (4) which are process impurities specific to the drug substance and are not included in the drug product specification). Degradants (b) (4) have structural alerts but were found by Ames testing to be negative for genotoxicity (see the separate review by the Pharmacology Toxicology team).

### **PHARMACOLOGY/TOXICOLOGY**

Please see Dr. Parvaneh Espandari's review document for detailed analysis.

The pharm/tox review indicates there are no novel excipients present in the drug product that would require non-clinical characterization. However, according to Dr. Espandiari, three active-ingredient-related (b) (4) impurities were identified that were determined to have structural alerts for mutagenic potential, which required qualification in bacterial reverse mutation (Ames) assays per ICH-M7. These impurities were negative in the Ames test both with and without metabolic activation in Salmonella typhimurium.

According to Dr. Espandiari, findings from nonclinical toxicity studies with members of the HMG-CoA reductase inhibitor class, in general, indicate the following are statin-related target organs: liver (elevated transaminases), kidney, gallbladder, rodent forestomach, muscle, lens of the eye, testicles, the central nervous system, and increased incidence of hepatic tumors (rodents). No safety signals indicative of unexpected or unmonitorable toxicity were observed in the 28-day rat toxicity study.

The pharmacology/toxicology team states that although the results from the 28-day rat toxicity study are of limited utility, it would not prohibit approval. From a nonclinical point of view, approval of the Applicant's formulation is reasonable, based on the findings from two clinical studies and analytical methods that establish that the Applicant's formulations meets Agency requirements as set forth in CMC-related guidance(s).

#### **FINANCIAL DISCLOSURE**

The sponsor provided a signed form FDA 3454, certifying that no financial arrangements or interests were held by the listed clinical investigators or the Applicant for the clinical pharmacology studies conducted to support approval of this application.

#### **PROPRIETARY NAME**

Lupin requested a review of the acceptability of the tradename Nikita. The Division of Medication Error Prevention and Analysis (DMEPA) has no objection to this proprietary name. In addition, the Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product.

#### **PEDIATRIC STUDY REQUIREMENTS**

Lupin requested a pediatric waiver for ages 0-16 for pitavastatin sodium. The Pediatric Review Committee (PeRC) and the Division of Metabolism and Endocrinology Products agreed with the waiver under the rationale that studies would be highly impractical to conduct in pediatric patients with non-familial dyslipidemia.

(b) (4)  
It is expected that pitavastatin sodium will eventually include the resulting pediatric labeling, once relevant exclusivities have expired.

## **RECOMMENDATIONS**

This reviewer recommends approval of this 505(b)(2) application for pitavastatin sodium. Labeling should reflect the approved pitavastatin calcium, Livalo.

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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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IFFAT N CHOWDHURY  
08/02/2017

JAMES P SMITH  
08/02/2017  
Concur with recommended regulatory action.