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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	209875
Supporting document/s:	SDN1, SN0000
Applicant's letter date:	10/21/2016
CDER stamp date:	10/21/2016
Product:	Pitavastatin Tablets (1, 2, and 4 mg)
Indication:	Primary hyperlipidemia or mixed dyslipidemia to reduce elevated total cholesterol, LDL-C, Apo B, and triglycerides, and to increase HDL-C
Applicant:	Lupin LTD
Review Division:	Division of Metabolism and Endocrinology Products
Reviewer:	Parvaneh Espandiari, PhD
Supervisor/Team Leader:	C. Lee Elmore, PhD
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1 Executive Summary

1.1 Introduction

Lupin LTD (the Applicant) proposes to market pitavastatin sodium tablets (Pitavastatin Tablets), 1mg, 2 mg, and 4 mg strengths, for the treatment of hyperlipidemia as a 505(b)(2) new drug application (NDA) with reliance on the FDA's finding of safety and effectiveness for the U.S.-approved, Orange Book-listed drug (LD) pitavastatin calcium tablets (Livalo®), marketed by Kowa under NDA 022363. The Applicant proposes to market Pitavastatin Tablets for the same indications and dosage regimens as that approved for the LD.

1.2 Brief Discussion of Nonclinical Findings

To support the approval of Pitavastatin Tablets, the Applicant conducted physicochemical analyses with the pitavastatin sodium drug substance and Pitavastatin Tablets product, a 28-day rat toxicity study with pitavastatin sodium, and two clinical bridging bioavailability/ bioequivalence studies comparing Pitavastatin Tablets to Livalo.

Physicochemical analyses established the absence of any impurities or degradants requiring qualification per ICH-Q3A and ICH-Q3B. However, 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. Please refer to the Pharmacology / Toxicology review in DMF (b) (4) for further details.

Excipients in the Pitavastatin Tablet formulation are deemed safe based on their inclusion in the Agency's Inactive Ingredient Database (IID) of prior U.S.-approved products that produce similar or greater exposures to each excipient, for chronic administration, and in comparable patient populations. No other concerns have been identified based on CMC characterization that would require additional safety assessments from a nonclinical point of view.

Pitavastatin Tablets were shown in clinical studies to be bioequivalent to the LD. There are no safety concerns for inclusion of very small quantities of sodium as the counter ion versus calcium in the LD.

A 28-day repeat-dose toxicity study was conducted in rats that compared the toxicities of pitavastatin sodium (i.e., the Pitavastatin Tablet drug substance) 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 LD). Thus, the study is considered to be of limited value. Toxicities observed with the Applicant's pitavastatin sodium formulation were typical of those generally known to occur in rodents with other statin drugs. No other useful information can be derived from this study.

The scientific bridge for reliance on the safety and effectiveness associated with the U.S. approved LD therefore primarily relied upon CMC and clinical bridging data. In the

absence of any outstanding nonclinical safety issues, the rat toxicity study is deemed unnecessary. Therefore, this deficiency is not considered by Pharmacology/Toxicology to be cause for recommendation against approval of Pitavastatin Tablets. No unmonitorable or otherwise concerning toxicities were observed in the 28-day rat toxicity study that would alter this assessment.

1.3 Recommendations

1.3.1 Approvability

Pharmacology/Toxicology recommends approval of this NDA for Pitavastatin Tablets. Product labeling should be identical to the PLLR compliant labeling for the LD, Livalo, marketed under NDA 022363.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The physicians insert (PI) for Livalo was recently brought into compliance with Pregnancy and Lactation Labeling Rule. We recommend the labeling for Pitavastatin Tablets be reproduced identically to the labeling for the LD, with the exception of the product Trade names.

Labeling Review

Reviewer's proposed label:

8.1 Pregnancy

NIKITA is contraindicated for use in pregnant women since safety in pregnant women has not been established and there is no apparent benefit to therapy with NIKITA during pregnancy. Because HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, NIKITA may cause fetal harm when administered to pregnant women. NIKITA should be discontinued as soon as pregnancy is recognized. Limited published data on the use of NIKITA are insufficient to determine a drug-associated risk of major congenital malformations or miscarriage. In animal reproduction studies, no embryo-fetal toxicity or congenital malformations were observed when pregnant rats and rabbits were orally administered pitavastatin during organogenesis at exposures which were 22 and 4 times, respectively, the maximum recommended human dose (MRHD) [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated

background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Human Data

Limited published data on pitavastatin have not reported a drug-associated risk of major congenital malformations or miscarriage. Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed the rate expected in the general population. The number of cases is adequate to exclude a greater than or equal to a 3- to 4-fold increase in congenital anomalies over background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified.

Animal Data

Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation. Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3, 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

8.2 Lactation

NIKITA is contraindicated during breastfeeding [see CONTRAINDICATIONS (4.4)]. There is no available information on the effects of the drug on the breastfed infant or the effects of the drug on milk production. However, it has been shown that another drug in

this class passes into human milk. Because of the potential for serious adverse reactions in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with NIKITA.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 92-week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors. In a 92-week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.

In a 26-week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30, 75, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.

Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.

Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 and 30 mg/kg/day, respectively, at systemic exposures 56- and 354-times clinical exposure at 4 mg/day based on AUC.

Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30-times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15-times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology
Central Nervous System Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended

dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons.

The section below must be removed because it is not in the PI of LD (Livalo).

2 Drug Information

2.2 Relevant INDs, NDAs, BLAs and DMFs

- DMF (b) (4) (pitavastatin sodium, Lupin)
- NDA 22363 (pitavastatin calcium, Livalo, Kowa)

2.3 Drug Formulation

Compositions of the Applicant's formulations (Pitavastatin sodium 1, 2, 4mg) are presented in the table below:

Table 1: Pitavastatin Tablets - Composition

Ingredients	1 mg Quantity mg/tablet	2 mg Quantity mg/tablet	4 mg Quantity mg/tablet	% w/w	Category	Reference to Standards
						(b) (4)
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)						NF
Hypromellose (b) (4)						USP
Sodium bicarbonate (b) (4)						USP
(b) (4)						USP
				(b) (4		
Low Substituted Hydroxypropyl Cellulose (b) (4)				(b) (4		NF
Magnesium Stearate (b) (4)						NF
				(b) (4)		--
				(b) (		
						IH
						USP
Total Weight of Coated Tablet (mg)	**82.400**	**164.800**	**329.600**	**100.00**	--	--

q.s: quantity sufficient

2.4 Comments on Novel Excipients

There are no novel excipients in the drug formulation. Excipients in the Pitavastatin Tablet formulation are deemed safe based on their inclusion in the Agency's Inactive Ingredient Database list of approved products that produce similar or greater exposures to each excipient, for chronic administration, and in comparable patient populations.

2.5 Comments on Impurities/Degradants of Concern

The Applicant refers to DMF (b) (4) (pitavastatin sodium) for the data supporting safety of three impurities with structural alerts for mutagenic potential, which were addressed per ICH-M7. Please refer to the Pharmacology / Toxicology review submitted to DMF (b) (4) for additional details.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet
Dosing Regimen: 1, 2, or 4 mg once daily

2.7 Regulatory Background

There was no Agency communication with the Applicant prior to NDA submission.

3 Studies Submitted

Study title: 28-Day Repeated Dose Oral (Gavage) Toxicity Study of Pitavastatin Sodium (LGP004) in Rat followed by 14-Day Recovery Phase (DSAG0289).

4 Pharmacology

4.1 Primary Pharmacology

No additional studies were required.

Pitavastatin is an inhibitor for the HMG-CoA reductase enzyme, which is involved in biosynthesis of cholesterol (rate-determining enzyme) in the liver. Reduction of cholesterol biosynthesis leads to upregulation of liver LDL-cholesterol receptor (LDLR). Increased LDLR expression leads to reduction in circulating LDL-cholesterol levels.

4.2 Secondary Pharmacology

No additional studies were required.

4.3 Safety Pharmacology

No additional studies were required.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No additional studies were required.

6 General Toxicology

6.2 Repeat-Dose Toxicity

A 28-day repeat-dose toxicity study was conducted by the Applicant, which was designed without feedback from the Agency. This study does not provide additional "bridging" toxicity information, because the Applicant's formulation was compared to a calcium salt form of pitavastatin with unknown safety characteristics compared to the approved LD (i.e., both the Applicant's formulation and the reference item were synthesized by the Applicant). The toxicity of small amounts of sodium counter ions (versus calcium ions) is not a significant safety concern.

However, the 28-day rat toxicity study with the Applicant's pitavastatin calcium drug substance at up to 10 mg/kg/day in rats was reviewed out of abundance of caution to compare the observed toxicities to those generally established to occur with statin treatment in rodent animal models to potentially rule out any unexpected and/or clinically unmonitorable toxicities associated with this new formulation.

Study title: 28-Day Repeated Dose Oral (Gavage) Toxicity Study of Pitavastatin Sodium (LGP004) in Rat followed by 14-Day Recovery Phase	
Study no.:	DSAG0289
Study report location:	eCTD
Conducting laboratory and location:	Lupin Limited (Research Park) Pune, India
Date of study initiation:	March 11, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Pitavastatin sodium; batch #: 410/SPJ/C-829/08; purity: 98.8 %

Key Study Findings

- Pitavastatin sodium was administered to Sprague Dawley rats by once daily oral (gavage) at 0 (vehicle), 2, 5, or 10 mg/kg/day versus 10 mg/kg pitavastatin calcium (also manufactured by Lupin).
- Groups administered HD pitavastatin (sodium or calcium) showed LFT increases, including AST (males) and ALT (males and females). In males, these changes were associated with histopathological changes in hepatocytes (minimal focal hepatocellular vacuolation).
- Histopathology samples were only analyzed for control and HD pitavastatin sodium and pitavastatin calcium (10 mg/kg/day) treated groups. Histopathologic changes consistent with statin-related effects were apparent in the liver (males, minimal focal hepatocellular vacuolation, 2/6 in HD vs. 1/6 in control); the kidney (males, minimal focal tubular mineralization of the renal papilla, 1/6 in HD vs. 0/6 in control, and cysts in the tubular cortex 1/6 in HD vs. 0/6 in control); in the heart (minimal focal mononuclear cell infiltration in the endocardium at HD in females, 1/6 in HD vs. 0/6 in control); and the lung (minimal focal granulomatous inflammation in alveoli, males 2/6 in HD vs. 0/6 in control and female 1/6 in HD vs. 0/6 in control).
- The NOAEL was established in this study at 10 mg/kg/day, based on the absence of clear, toxicologically significant statin-related toxicity at that dose.
    - The human relevance of this assignment of a NOAEL is confounded by the lack of toxicokinetic evaluation; the actual statin exposures (by AUC) in this study, which are necessary to make accurate comparisons to human exposures, are unknown.
    - However, dose-related increases in LFTs implies statin exposure occurred; in the absence of new or concerning toxicities compared to established statin-related toxicities in rodents, the results do not raise any concerns regarding the safety of pitavastatin sodium with respect to impurities and/or degradants at up to approximately 23-fold the human pitavastatin exposure (based on body surface area extrapolations).

Methods	
Doses:	Pitavastatin sodium: 0 (vehicle), 2, 5, 10 mg/kg/day Reference pitavastatin calcium: 10 mg/kg/day
Frequency of dosing:	Once daily for 28 days
Route of administration:	Oral (gavage)
Dose volume:	10 mL/kg
Formulation/Vehicle:	Tween 80 (1% v/v) and 0.5% w/v Carboxymethyl cellulose solution (1:99)
Species/Strain:	Rats/Sprague Dawley
Number/Sex/Group:	HD and control: 11/sex/group LD and MD: 6/sex/group
Age:	6-7 weeks

Weight:	199.2 - 238.4 (Male); 172.1 - 212.7 (Female)
Satellite groups:	9/sex/group
Deviation from study protocol:	No significant deviations were reported.

Table 2: Experimental Design

Test/ Reference Item	Group	Dose Level (mg/kg/day)	Conc. (mg/mL)	Number of animals		Animal Number	
				Male	Female	Male	Female
Toxicity Animals							
NA	1 (Control)[a, b]	0	0.0	11	11	1-11	46-56
Test Item: Pitavastatin Sodium (LGP004)	2 (Low)	2	0.2	6	6	12-17	57-62
	3 (Mid)	5	0.5	6	6	18-23	63-68
	4 (High)[b]	10	1.0	11	11	24-34	69-79
Reference Item: Pitavastatin Calcium (LGP003)	5 (Reference Item)[b]	10	1.0	11	11	35-45	80-90
Toxicokinetic Animals							
Test Item: Pitavastatin Sodium (LGP004)	6 (High)	10	1.0	9	9	91-99	109-117
Reference Item: Pitavastatin Calcium (LGP003)	7 (Reference Item)	10	1.0	9	9	100-108	118-126

a - Group 1 received vehicle control only.
b – Up to 6 animals/gender were sacrificed after 28 days of dosing and up to 5 animals/gender, were sacrificed after 28 days of dosing and 14-day recovery phase.
Note - Dose formulations for Group 4 and 6, Group 5 and 7 were prepared together.

Note: In this study, the U.S. -approved LD was not used. Both the Applicant's formulation and the reference item were synthesized and supplied by the (b) (4)

Observations and Results

Mortality

No mortality occurred.

Clinical Signs

No treatment-related findings were observed.

Body Weights

No treatment-related findings were observed.

Feed Consumption

No treatment-related findings were observed.

Ophthalmoscopy

No treatment-related findings were observed.

Hematology

Treatment-related changes in hematology parameters are as follows:

- At ≥ 5 mg/kg/day (MD), in males, increased neutrophil and decreased lymphocytes were reported in treated animals as well as in pitavastatin calcium-treated group.

- Decreased eosinophil count was noted in all treated males and in the pitavastatin calcium group in males.
- In females, prothrombin times increased in a dose-related manner. No unusual episodes of bleeding were observed in the study.

Tables below were modified from the Applicant's submitted summary tables:

Males

Para-meters	Group No. & Dose (mg/kg/day)														
	G1(0)			G2 (2)			G3 (5)			G4 (10)			G5 (10)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Nu (%)	16.22	4.44	11	20.68	2.98	6	23.53↑	6.60	6	23.24↑	4.74	11	25.65↑↑↑	6.82	11
Ly (%)	80.88	4.74	11	76.53	5.26	6	73.72	7.75	6	71.69↓	6.75	11	70.26↓↓	8.66	11
Es (%)	0.28	0.41	11	0.04	0.01	6	0.04	0.03	6	0.03↓	0.04	11	0.04↓	0.04	11

Key:,↑= Significantly higher than control ($P < 0.05$), , ↑↑↑= Significantly higher than control ($P < 0.001$),
↓=significantly lower than control ($P < 0.05$), ↓↓= Significantly lower than control ($P < 0.01$)

Females

Para-meters	Group No. & Dose (mg/kg/day)														
	G1(0)			G2 (2)			G3 (5)			G4 (10)			G5 (10)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
MCHC (g/dL)	38.53	0.57	11	38.55	0.27	6	38.45	0.22	6	39.02	0.58	11	39.10↑	0.46	11
PT (Sec)	15.87	0.84	11	16.27	0.52	6	17.05↑	0.76	6	17.25↑↑↑	0.74	11	16.53	0.79	11

Key: ↑= Significantly higher than control ($P < 0.05$), ↑↑↑= Significantly higher than control ($P < 0.001$)

Note: Anti-inflammatory effects of statins have been shown with several statins.

Clinical Chemistry

Treatment-related changes in clinical chemistry parameters are as follows:

- Doses ≥ 2 mg/kg/day pitavastatin sodium or calcium induced decreases in triglyceride levels (males-only) that was also noted in recovery groups.
  At the HD, decreased in levels of sodium (males), increased in levels of aspartate aminotransferase (males), and Increased in levels of alanine aminotransferase (males and females) were reported in animals administered pitavastatin sodium or calcium.
- Liver enzymes changes in males were associated with minimal focal hepatocellular vacuolation). See the following Applicant tables:

Males:

Para-meters	Group No. & Dose (mg/kg/day)														
	G1(0)			G2 (2)			G3 (5)			G4 (10)			G5 (10)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
ALT (IU/L)	48.04	7.34	11	48.05	9.68	6	53.12	7.50	6	69.67↑	21.13	11	68.18↑	21.75	11
AST (IU/L)	88.07	20.46	11	93.28	11.37	6	100.85	13.92	6	142.25↑	39.43	11	156.43↑↑	87.39	11
TGL (mg/dL)	38.11	17.02	11	16.15↓↓	5.72	6	31.23	17.32	6	17.90↓↓	9.07	11	14.85↓↓↓	12.10	11

Key: ↑= Significantly higher than control ($P < 0.05$), ↓= Significantly lower than control ($P < 0.05$), ↓↓= Significantly lower than control ($P < 0.01$),), ↑↑= Significantly higher than control ($P < 0.01$), ↓↓↓= Significantly lower than control ($P < 0.001$)

Females:

Para-meters	Group No. & Dose (mg/kg/day)														
	G1(0)			G2 (2)			G3 (5)			G4 (10)			G5 (10)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
ALT (IU/L)	38.57	4.23	11	43.37	6.70	6	49.13	11.70	6	53.54↑	12.17	11	49.68	17.61	11
AST (IU/L)	81.62	19.81	11	85.60	14.94	6	94.40	17.39	6	100.38	15.33	11	102.95↑	22.39	11

Key: ↑= Significantly higher than control ($P < 0.05$).

Urinalysis

No treatment-related findings were observed.

Gross Pathology

No-treatment related changes were noted.

Organ Weights

No significant organ weight changes were observed in treated animals. At 5mg/kg/day (MD), in females, decreased in absolute and relative heart weight was reported, but this finding was not dose-related and did not correlate to any histopathological findings. This finding was therefore considered likely to be incidental.

Histopathology

Adequate Battery: Yes. However, only control and the HD statin-treated data were reported.
Peer Review: Not specified.
Changes in HD treated animals versus those administered the vehicle control consistent with statin treatment was observed in:

- Liver: in males, focal minimal vacuolation hepatocellular (2/6 vs. 1/6 in control)
- Kidney: in males, focal minimal mineralization tubular renal papilla (1/6 vs. 0/6 in control) and cyst tubular cortex (1/6 vs. 0/6 in control)
- Heart, in females, focal minimal infiltration mononuclear cells endocardium (1/6 vs. 0/6 in control)
- Lung, focal minimal inflammation granulomatous alveolar (males, 2/6 vs. 0/6 in control; females 1/6 vs. 0/6 in control)

The following are Applicant's tables:

Table 3: Summary of Histopathology Observations

Fate: Terminal sacrifice **Gender: Male & Female**

Organ	Histopathology Observations	Distribution	Severity	Group and Dose (mg/kg/day)					
				Male			Female		
				G1 (0)	G4 (10)	G5 (10)	G1 (0)	G4 (10)	G5 (10)
Liver	infiltration, MNC, perivascular	focal	minimal	2/6	2/6	2/6	4/6	1/6	2/6
		multifocal	minimal	-	-	-	-	2/6	1/6
			Total	2/6	2/6	2/6	4/6	3/6	3/6
	vacuolation, hepatocellular	focal	minimal	1/6	2/6	-	-	-	-
	necrosis, hepatocellular,	focal	minimal	-	-	1/6	1/6	-	-
	necrosis, hepatocellular, subcapsular	focal	minimal	-	-	1/6	1/6	-	-
Kidneys	mineralization, tubular, corticomedullary junction	focal	minimal	-	-	-	2/6	2/6	1/6
		multifocal	minimal	-	-	-	-	-	1/6
			Total	-	-	-	2/6	2/6	2/6
	mineralization, tubular, renal papilla,	focal	minimal	-	1/6	-	-	-	-
	cyst, tubular, cortex	present	-	-	1/6	-	-	-	-
Adrenals	vacuolation, zona fasciculata	multifocal	minimal	1/6	-	-	-	-	-
	accessory adrenal tissue	present		1/6	1/6	-	-	-	1/6
Heart	infiltration, MNC, pericardial	focal	minimal	2/6	-	-	-	-	-
	infiltration, MNC, myocardial	focal	minimal	-	1/6	-	-	-	1/6
	infiltration, MNC, endocardium	focal	minimal	-	-	-	-	1/6	-
Brain	cortex, mineralization, perivascular	focal	minimal	1/6	-	-	-	-	-
Thyroid	ectopic thymus tissue	present	-	1/6	1/6	-	-	-	-
	infiltration, PMNC & MNC, interstitial	focal	minimal	-	-	-	-	1/6	-

Fate: Terminal sacrifice **Gender: Male & Female**

Organ	Histopathology Observations	Distribution	Severity	Group and Dose (mg/kg/day)					
				Male			Female		
				G1 (0)	G4 (10)	G5 (10)	G1 (0)	G4 (10)	G5 (10)
Eyes	retinal fold, unilateral,	present	-	1/6	-	-	-	1/6	-
	infiltration, MNC, retinal inner nuclear layer, (unilateral)	diffuse	minimal	-	-	-	-	-	1/6
	discreet cell loss retinal inner nuclear layer, (unilateral)	diffuse	minimal	-	-	-	-	-	1/6
Trachea	infiltration, MNC, submucosa	focal	minimal	3/6	1/6	1/6	-	-	-
		multifocal	minimal	1/6	-	-	-	-	-
		focal	mild	-	-	-	2/6	2/6	
Thymus	lymphocytolysis, cortical	multifocal	minimal	2/6	4/6	4/6	5/6	2/6	2/6
		multifocal	mild	-	1/6	-	-	-	-
			Total	2/6	5/6	4/6	5/6	2/6	2/6
	thymopharyngeal duct, remnants	present	-	-	-	-	1/6	-	-
	congestion, cortex and medulla	focal	minimal	-	-	-	-	1/6	-
	fibrous connective tissue proliferation, pericapsular	multifocal	mild	1/6	-	-	-	-	-
Lungs	infiltration, MNC, perivascular	focal	minimal	-	-	-	-	3	3
		multifocal	minimal	1/6	1/6	3/6	4/6	-	1/6
		multifocal	mild	2/6	3/6	1/6	-	1/6	-
			Total	3/6	4/6	4/6	4/6	4/6	4/6
	infiltration, MNC, perivascular/ peribronchiolar	multifocal	minimal	-	-	-	1/6	2/6	-
	histiocytosis, alveolar	focal	minimal	1/6	1/6	1/6	-	1/6	-
		multifocal	mild	-	-	-	-	-	1/6
			Total	1/6	1/6	1/6	-	1/6	1/6

Fate: Terminal sacrifice **Gender: Male & Female**

Organ	Histopathology Observations	Distribution	Severity	Group and Dose (mg/kg/day)					
				Male			Female		
				G1 (0)	G4 (10)	G5 (10)	G1 (0)	G4 (10)	G5 (10)
Lungs (continued)	mineralization, vascular	focal	minimal	1/6	-	1/6	-	-	-
	inflammation, granulomatous, alveolar	focal	minimal	-	2/6	2/6	-	1/6	1/6
		focal	mild	-	-	-	-	1/6	-
			Total	-	2/6	2/6	-	2/6	1/6
	lympho proliferation, bronchial associated lymphoid tissue	focal	mild	-	-	1/6	-	-	-
Urinary bladder	infiltration, MNC, submucosa	focal	minimal	1/6	-	-	-	-	-
Esophagus	infiltration, MNC, muscularis layer	focal	minimal	-	-	1/6	-	-	-
Duodenum	infiltration, MNC, epithelial	focal	minimal	1/6	1/6	2/6	1/6	-	-
Pancreas	increased apoptosis, acinar cells	multifocal	mild	1/6	1/6	-	-	-	-
Prostate	infiltration, MNC, interstitial	multifocal	mild	2/6	-	-	x	x	x
Seminal Vesicle	exfoliation, acinar cell epithelium in lumen	focal	mild	1/6	-	-	x	x	x

Keys: '-' Lesion not observed, 'x'- organ not present due to gender difference

Note: All study plan defined organs/tissues examined microscopically for G1, G4 and G5 animals. Organs / tissue (Spleen, Pituitary gland, Lymph Nodes-mandibular, Salivary glands-mandibular, Parathyroid, Aorta, Skin, Skeletal muscle, Sciatic Nerves, Optic Nerves, Stomach, Jejunum, Ileum, Cecum, Colon, Lymph Nodes-Mesenteric, Rectum, Sternum with bone marrow, Femur with bone marrow, Spinal cord (Cervical, Thoracic, Lumbar), Harderian gland, Female mammary gland, Testes, Epididymis, Ovary, Uterus, Cervix and Vagina showed normal histological architecture and minor variations were considered within normal range of histology limits.

Toxicokinetics

Samples for TK data were collected, but were not analyzed.

Dosing Solution Analysis

According to the Applicant: “The results of dose formulation analysis for Pitavastatin Sodium (LGP004) for 0.2 mg/mL, 0.5 mg/mL and 1 mg/mL and Pitavastatin Calcium (LGP003) for 1mg/mL were within ± 15 % of target concentration on prior to dosing and were considered homogenous and stable up to 24 hours at room temperature”.

7 Genetic Toxicology

No genotoxicity studies were required.

From LD labeling:
“Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test, clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity”.

8 Carcinogenicity

No carcinogenicity studies were required.

From LD labeling:
“13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 92-week carcinogenicity study in mice given pitavastatin, at the maximum tolerated dose of 75 mg/kg/day with systemic maximum exposures (AUC) 26 times the clinical maximum exposure at 4 mg/day, there was an absence of drug-related tumors. In a 92-week carcinogenicity study in rats given pitavastatin at 1, 5, 25 mg/kg/day by oral gavage there was a significant increase in the incidence of thyroid follicular cell tumors at 25 mg/kg/day, which represents 295 times human systemic exposures based on AUC at the 4 mg/day maximum human dose.
In a 26-week transgenic mouse (Tg rasH2) carcinogenicity study where animals were given pitavastatin at 30, 75, and 150 mg/kg/day by oral gavage, no clinically significant tumors were observed.
Pitavastatin was not mutagenic in the Ames test with *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation, the micronucleus test following a single administration in mice and multiple administrations in rats, the unscheduled DNA synthesis test in rats, and a Comet assay in mice. In the chromosomal aberration test,

clastogenicity was observed at the highest doses tested which also elicited high levels of cytotoxicity.
Pitavastatin had no adverse effects on male and female rat fertility at oral doses of 10 and 30 mg/kg/day, respectively, at systemic exposures 56- and 354-times clinical exposure at 4 mg/day based on AUC.
Pitavastatin treatment in rabbits resulted in mortality in males and females given 1 mg/kg/day (30-times clinical systemic exposure at 4 mg/day based on AUC) and higher during a fertility study. Although the cause of death was not determined, rabbits had gross signs of renal toxicity (kidneys whitened) indicative of possible ischemia. Lower doses (15-times human systemic exposure) did not show significant toxicity in adult males and females. However, decreased implantations, increased resorptions, and decreased viability of fetuses were observed.

13.2 Animal Toxicology and/or Pharmacology
Central Nervous System Toxicity
CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Wallerian degeneration has not been observed with pitavastatin. Cataracts and lens opacities were seen in dogs treated for 52 weeks at a dose level of 1 mg/kg/day (9 times clinical exposure at the maximum human dose of 4 mg/day based on AUC comparisons.

9 Reproductive and Developmental Toxicology

No reproductive and development studies were required.

From LD labeling:
“8.1 Pregnancy
Teratogenic effects: Pregnancy Category X
LIVALO Pitavastatin is contraindicated in women who are or may become pregnant. Serum cholesterol and TG increase during normal pregnancy, and cholesterol products are essential for fetal development. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hyperlipidemia therapy [see Contraindications (4)]. There are no adequate and well-controlled studies of LIVALO pitavastatin in pregnant women, although, there have been rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of about 100 prospectively followed pregnancies in women exposed to other HMG-CoA reductase inhibitors, the incidences of congenital anomalies, spontaneous abortions, and fetal

deaths/stillbirths did not exceed the rate expected in the general population. However, this study was only able to exclude a three-to-four-fold increased risk of congenital anomalies over background incidence. In 89% of these cases, drug treatment started before pregnancy and stopped during the first trimester when pregnancy was identified. Reproductive toxicity studies have shown that pitavastatin crosses the placenta in rats and is found in fetal tissues at ≤36% of maternal plasma concentrations following a single dose of 1 mg/kg/day during gestation. (b) (4)

Embryo-fetal developmental studies were conducted in pregnant rats treated with 3, 10, 30 mg/kg/day pitavastatin by oral gavage during organogenesis. No adverse effects were observed at 3 mg/kg/day, systemic exposures 22 times human systemic exposure at 4 mg/day based on AUC.

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

Embryo-fetal developmental studies were conducted in pregnant rabbits treated with 0.1, 0.3, 1 mg/kg/day pitavastatin by oral gavage during the period of fetal organogenesis. Maternal toxicity consisting of reduced body weight and abortion was observed at all doses tested (4 times human systemic exposure at 4 mg/day based on AUC).

In perinatal/postnatal studies in pregnant rats given oral gavage doses of pitavastatin at 0.1, 0.3, 1, 3, 10, 30 mg/kg/day from organogenesis through weaning, maternal toxicity consisting of mortality at ≥0.3 mg/kg/day and impaired lactation at all doses contributed to the decreased survival of neonates in all dose groups (0.1 mg/kg/day represents approximately 1 time human systemic exposure at 4 mg/day dose based on AUC).

Pitavastatin may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking pitavastatin, the patient should be apprised of the potential risks to the fetus and the lack of known clinical benefit with continued use during pregnancy.

(b) (4)

11 Integrated Summary and Safety Evaluation

The Applicant seeks approval of Pitavastatin Tablets (1mg, 2mg, 4 mg) for the treatment of hypercholesterolemia as a 505(b)(2) new drug application with reliance on the prior findings of safety and effectiveness as the approved listed drug (LD) Livalo® (Pitavastatin tablets, NDA 022363). Both the Applicant's product and the LD would have same indications and dosage regimens.

The HMG-CoA reductase inhibitors (statins) are the first-line drugs for cholesterol reduction. In clinical studies, statins have been shown to reduce plasma cholesterol (LDL-C) and decrease the incidence of major cardiovascular events such as death, stroke, myocardial infarction, and coronary revascularization. Adverse reactions with pitavastatin and with statins in general are well known and may include myalgia, myopathy, rhabdomyolysis and liver transaminase elevation.

To establish a "bridge" between the Applicant's formulation and the LD, two bioavailability/bioequivalence clinical studies were completed (with the Applicant's formulation and Livalo) and detailed CMC information for Pitavastatin Tablets were provided. The Applicant also conducted a 28-Day rat toxicity study (with Applicant's formulation to the calcium salt form of Pitavastatin).

The design of the 28-Day rat toxicity study limited its effectiveness for supporting the 505(b)(2) regulatory pathway, because the study compared the toxicity profiles of pitavastatin sodium to the Applicant's own preparation of pitavastatin calcium instead of the approved LD (i.e., Livalo®). The Applicant reported that "Lupin has used Sodium salt of Pitavastatin as a drug substance instead of Calcium salt of Pitavastatin used by RLD as permitted by 505(b)(2) pathway, hence Pitavastatin Sodium contains slight differences in general properties compare to Pitavastatin Calcium. Difference in inactive ingredient used i.e. Sodium Bicarbonate is used instead of Magnesium Aluminometasilicate used by RLD [sic] and it used (b) (4) ". Moreover, the toxicokinetic samples from treated rats were collected, but were not analyzed. Therefore, pitavastatin exposures (by AUC) are unknown, but could only be estimated based on body surface area extrapolation. For the reasons discussed, this study was of limited utility. However, given that an acceptable scientific bridge was established with clinical information and CMC evaluations, a nonclinical bridging study was deemed to be unnecessary to support this particular NDA.

Three impurities were determined by the CMC team to have structural alerts for mutagenic potential. These concerns were addressed per ICH-M7. These impurities were negative in GLP compliant batteries of Ames tests both with and without metabolic activation in Salmonella typhimurium strains. Please refer to the Pharmacology/ Toxicology review submitted to DMF (b) (4) for additional details.

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).

In conclusion, the results from the 28-day rat toxicity study are of limited utility to support marketing approval of Pitavastatin Tablets. However, from a nonclinical point of view, approval of the Applicant's formulation is reasonable, based on the findings from two clinical studies (bioavailability/bioequivalence) and analytical methods that establish that the Applicant's formulations meets Agency requirements as set forth in CMC-related guidance(s). No safety signals indicative of unexpected or unmonitorable (compared to statins) toxicity were observed in the 28-day rat toxicity study.

12 Appendix/Attachments

Below communication was send to the Applicant with the 45 days filing:

"Comment for potential review issues to the Applicant for the 74-day letter: Your NDA contains a 28-day bridging rat study comparing the toxicity of two different salt forms of pitavastatin, pitavastatin sodium (the proposed drug) and pitavastatin calcium (produced in-house). The safety concern regarding substitution of the calcium counterion of the listed drug Livalo with sodium is minimal. 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. Whether or not the clinical, CMC and other nonclinical data are sufficient to establish an acceptable scientific bridge between your proposed pitavastatin sodium product and that of the listed drug Livalo is a review issue".

Below email from the Applicant was received on January 2017:

From: Sudhir Kaushal [mailto:skaushal@lupinusa.com]
Sent: Wednesday, January 04, 2017 9:53 AM
To: Whitehead, Richard
Subject: NDA#209875#Pitavastatin Tablets-Acknowledgement/ Filing Review Issues Identified letter
Good Morning Mr. Whitehead,

Today I am contacting you regarding the acknowledgement letter received for our NDA 209875 where in the Agency has indicated that there can be a potential review issue related to the nonclinical, rat toxicity study. We would like to present our justification, for the current design of the rat-toxicity study. Please see below.
We have designed this toxicity study without the use of reference product, Livalo as safety of reference product has been established and well documented in different nonclinical species. (NDA 22-363, Pitavastatin, (Livalo®). As per Verbeeck et al (2006), toxicity studies are required for a new salt form of an active substance when the salt of

that active substance has been prepared by using a new salt-forming agent with little or no information on its toxicity profile. Sodium salts are not considered in this context due to the endogenous nature of sodium, with a dietary reference intake level of 1.3 g for 19–70 year old adults recommended from the Institute of Medicine of the U.S. National Academy of Sciences (Institute of Medicine, 2013) (Saal et al, 2013).
Further, many pharmaceutical drugs as sodium salt (oral & injectable) has been approved and being used safely in human.
In light of this information, objective of this 28 day toxicity study was to characterize the toxicity (if any) of pitavastatin as a sodium salt as compared to calcium salt at similar dose levels and under similar experimental conditions. Nevertheless, no significant differences were noted among study plan defined parameters of pitavastatin sodium treated and vehicle control groups [i.e. Tween 80 (1% v/v): 0.5% w/v Carboxymethyl cellulose solution]. In the event of comparable results with vehicle control group the use of a reference control holds minimal value in the interpretation of the study results".
In view of above, in our opinion, new study with inclusion of Livalo (RLD) instead of in house pitavastatin calcium in the bridging toxicity study seems to be not warranted. However, we seek agency's advice for our understanding of acceptance or justification that, we need not to consider this as a potential review issue.
Thanks & regards,

Sudhir Kaushal, RAC
Director, Regulatory Affairs
Lupin Pharmaceuticals Inc.
Direct line: 443-740-9337
Office: 410-576-2000 Ext. 2338
Cell no: (b) (6)

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

/s/

PARVANEH ESPANDIARI
06/26/2017

CALVIN L ELMORE
06/27/2017
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 209875	**Applicant:** Lupin LTD	**Stamp Date:** 10/21/2016
Drug Name: Pitavastatin Tablets (1mg, 2mg, 4mg)	**NDA Type:** 505(b)(2)	**Indication:** Hyperlipidemia

Regulatory History: Pitavastatin Tablets are being developed by Lupin for the treatment of hyperlipidemia as an adjunctive therapy to diet. To support this 505(b)(2) NDA application, the Applicant is relying on FDA's finding of safety and effectiveness for approved listed drug (LD) Livalo® (Pitavastatin tablets; NDA 22363). Both the Applicant's drug product and the LD have the same active ingredient. To establish a "bridge" between these two formulations, the Applicant conducted clinical (bioavailability/bioequivalence) and pre-clinical studies.

On **initial** overview of the NDA application for filing: The NDA appears fileable from a Pharm/Tox point of view.

	Content Parameter	Yes	No	Comment
	s the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The eCTD submission has 5 modules – regional (forms) for common technical document summary, quality (CMC), nonclinical study reports (pharm/tox), and clinical study reports (clinical trials).
2	s the pharmacology/toxicology section ndexed and paginated in a manner allowing substantive review to begin?	X		
3	s the pharmacology/toxicology section egible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 ncluding referenced literature) completed and submitted carcinogenicity, mutagenicity, teratogenicity, effects on fertility, uvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		To support 505(b)(2) application, the Applicant is relying on FDA's finding of safety and effectiveness for approved LD, Livalo®. To establish a "bridge" between the applicant's formulation and the LD formulation, a rat study (28 days with 14 days recovery period) was conducted with both formulations. Carcinogenicity studies have been conducted previously with Pitavastatin.
5	f the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted ith appropriate formulations? (For other than the oral route, some studies	X		The rat toxicity study was conducted with the same formulation and the route of the administration that are planned to be marketed.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
	may be by routes different from the clinical route intentionally and by desire of the FDA).			
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			n/a (no PIND/IND; no previous communication).
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		The draft labeling submitted is not in PLLR (similar to the approved LD).
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	X		The drug substance impurities were referred to DMF (b) (4) (Pitavastatin Sodium).
11	Has the applicant addressed any abuse potential issues in the submission?			n/a.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			n/a.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____Yes____

Comment for potential review issues to the Applicant for the 74-day letter:
Your NDA contains a 28-day bridging rat study comparing the toxicity of two different salt forms of pitavastatin, pitavastatin sodium (the proposed drug) and pitavastatin calcium (produced in-house). The safety concern regarding substitution of the calcium counter-ion of the listed drug Livalo with sodium is minimal. 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. Whether or not the clinical, CMC and other nonclinical data are sufficient to establish an acceptable scientific bridge between your proposed pitavastatin sodium product and that of the listed drug Livalo is a review issue.

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

PARVANEH ESPANDIARI
12/06/2016

CALVIN L ELMORE
12/06/2016