CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209875Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209875
Link to EDR	\\CDSESUB1\evsprod\NDA209875\0000
Submission Date	10/21/2016
Submission Type	505 (b)(2), standard review
Brand Name	Nikita
Generic Name	Pitavastatin Sodium
Dosage Form and Strength	Immediate Release Tablets (1 mg, 2 mg, 4 mg)
Route of Administration	Oral
Proposed Indication	• Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol. • Limitations of use: o Do not exceed 4 mg once daily dosing of pitavastatin o The effect on cardiovascular morbidity and mortality has not been determined o Pitavastatin has not been studied in Fredrickson Type I, III, and V dyslipidemias.
Applicant	Lupin Limited
Associated IND	NA
OCP Review Team	Lei He, PhD
OCP Final Signatory	Jayabharathi Vaidyanathan, PhD (Team Leader)

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1. EXECUTIVE SUMMARY

Pitavastatin inhibits cholesterol synthesis in the liver by competitively inhibiting HMG-CoA reductase. On August 3, 2009, LIVALO® (pitavastatin) tablet (calcium salt; strengths of 1 mg, 2 mg, and 4 mg, equivalent to 1 mg, 2 mg, and 4 mg pitavastatin, respectively) from Kowa Pharmaceuticals America, Inc. was approved by the FDA under NDA 022363 for the treatment of primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol.

On October 21, 2016, Lupin Limited submitted this NDA application seeking the approval of pitavastatin tablet (sodium salt; strengths of 1 mg, 2 mg, and 4 mg, equivalent to 1 mg, 2 mg, and 4 mg pitavastatin, respectively) via 505(b)(2) pathway using LIVALO® (pitavastatin) tablet as reference product, and proposing the same dosage, route of administration, and indications as LIVALO®. There is no previous communication between Lupin Limited and the Agency before the NDA submission.

Two clinical studies, Study LBC-ARL/16/056 and Study LBC-ARL/16/057, were conducted under this NDA to demonstrate the bioequivalence (BE) between the test product (4 mg pitavastatin tablet (sodium salt)) and the reference product (4mg LIVALO® (pitavastatin) tablet (calcium salt)) under fasting and fed conditions, respectively. Results indicate that 4 mg pitavastatin tablet is bioequivalent to 4mg LIVALO® (pitavastatin) tablet under both fasting and fed conditions. Sponsor has requested biowaiver for the lower strength tablets (1 mg and 2 mg).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 209875 Clinical Pharmacology data and recommends approval.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Pitavastatin inhibits cholesterol synthesis in the liver by competitively inhibiting HMG-CoA reductase.

This NDA application for pitavastatin tablet (sodium salt; strengths of 1 mg, 2 mg, and 4 mg) was submitted via 505(b)(2) pathway using LIVALO® (pitavastatin) tablet as reference product. Two BE studies were conducted in healthy subjects comparing the test product (4 mg pitavastatin tablet) and the reference product (4mg LIVALO® (pitavastatin) tablet) under fasting and fed conditions, respectively. PK results from both studies indicate that, following the single oral administration of 4 mg pitavastatin tablet and LIVALO® (pitavastatin) tablet, the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf of pitavastatin are all well within

80-125%, suggesting that 4 mg pitavastatin tablet is bioequivalent to 4mg LIVALO® (pitavastatin) tablet under both fasting and fed conditions.

Sponsor has requested biowaiver for 1 mg and 2 mg pitavastatin tablets. Refer to the Biopharm Review for more detailed information.

2.2 Dosing Regimen

The proposed dosing regimen for pitavastatin tablets is the same as LIVALO® (pitavastatin) tablet.

- Pitavastatin tablets can be taken with or without food, at any time of day. Dose Range: 1 mg to 4 mg once daily.
- Primary hyperlipidemia and mixed dyslipidemia: Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day.
- Moderate and severe renal impairment (glomerular filtration rate 30 to 59 and 15 to 29 mL/min/1.73 m^2, respectively) as well as end-stage renal disease on hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

For Section 12.3, the information from BE studies under this NDA was recommended to be removed.

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

(b) (4)

Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both C_{max} and $AUC_{0\text{-}inf}$ increased in an approximately dose-proportional manner for single pitavastatin doses from 1 to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of pitavastatin with a high fat meal (50% fat content) decreases pitavastatin C_{max} by 43% but does not significantly reduce pitavastatin AUC. The C_{max} and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution
Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism
Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion
A mean of 15% of radioactivity of orally administered, single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

Race
In pharmacokinetic studies pitavastatin C_{max} and AUC were 21 and 5% lower, respectively in Black or African American healthy volunteers compared with those of Caucasian healthy volunteers. In pharmacokinetic comparison between Caucasian volunteers and Japanese volunteers, there were no significant differences in C_{max} and AUC.

Gender
In a pharmacokinetic study which compared healthy male and female volunteers, pitavastatin C_{max} and AUC were 60 and 54% higher, respectively in females. This had no effect on the efficacy or safety of pitavastatin in women in clinical studies.

Geriatric
In a pharmacokinetic study which compared healthy young and elderly (≥65 years) volunteers, pitavastatin C_{max} and AUC were 10 and 30% higher, respectively, in the elderly. This had no effect on the efficacy or safety of pitavastatin in elderly subjects in clinical studies.

Renal Impairment
In patients with moderate renal impairment (glomerular filtration rate of 30 to 59 mL/min/ 1.73 m^2) and end stage renal disease receiving hemodialysis, pitavastatin $AUC_{0\text{-}inf}$ is 102 and 86% higher than those of healthy volunteers, respectively, while pitavastatin C_{max} is 60 and 40% higher than those of healthy volunteers, respectively. Patients received hemodialysis immediately before pitavastatin dosing and did not undergo hemodialysis during the pharmacokinetic study. Hemodialysis patients have 33 and 36% increases in the mean unbound fraction of pitavastatin as compared to healthy volunteers and patients with moderate renal impairment, respectively.

In another pharmacokinetic study, patients with severe renal impairment (glomerular filtration rate 15 to 29 mL/min/1.73 m^2) not receiving hemodialysis were administered a single dose of pitavastatin 4 mg. The

$AUC_{0\text{-}inf}$ and the C_{max} were 36 and 18% higher, respectively, compared with those of healthy volunteers. For both patients with severe renal impairment and healthy volunteers, the mean percentage of protein-unbound pitavastatin was approximately 0.6%.

The effect of mild renal impairment on pitavastatin exposure has not been studied.

Hepatic Impairment

The disposition of pitavastatin was compared in healthy volunteers and patients with various degrees of hepatic impairment. The ratio of pitavastatin C_{max} between patients with moderate hepatic impairment (Child-Pugh B disease) and healthy volunteers was 2.7. The ratio of pitavastatin AUC_{inf} between patients with moderate hepatic impairment and healthy volunteers was 3.8. The ratio of pitavastatin C_{max} between patients with mild hepatic impairment (Child-Pugh A disease) and healthy volunteers was 1.3. The ratio of pitavastatin AUC_{inf} between patients with mild hepatic impairment and healthy volunteers was 1.6. Mean pitavastatin $t_{½}$ for moderate hepatic impairment, mild hepatic impairment, and healthy were 15, 10, and 8 hours, respectively.

Drug-Drug Interactions

The principal route of pitavastatin metabolism is glucuronidation via liver UGTs with subsequent formation of pitavastatin lactone. There is only minimal metabolism by the cytochrome P450 system.

Warfarin

The steady-state pharmacodynamics (international normalized ratio [INR] and prothrombin time [PT]) and pharmacokinetics of warfarin in healthy volunteers were unaffected by the co-administration of pitavastatin 4 mg daily. However, patients receiving warfarin should have their PT time or INR monitored when pitavastatin is added to their therapy.

Table 2. Effect of Co-Administered Drugs on Pitavastatin Systemic Exposure

Co-administered drug	Dose regimen	Change in AUC*	Change in C_{max}*
Cyclosporine	Pitavastatin 2 mg QD for 6 days + cyclosporine 2 mg/kg on Day 6	↑ 4.6 fold†	↑ 6.6 fold †
Erythromycin	Pitavastatin 4 mg single dose on Day 4 + erythromycin 500 mg 4 times daily for 6 days	↑ 2.8 fold †	↑ 3.6 fold †
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days	↑ 29%	↑ 2.0 fold
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days	↑ 31%	↑ 60%
Darunavir/Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16	↓ 26%	↓4%
Lopinavir/Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24	↓ 20%	↓4 %
Gemfibrozil	Pitavastatin 4 mg QD + gemfibrozil 600 mg BID for 7 days	↑ 45%	↑ 31%
Fenofibrate	Pitavastatin 4 mg QD + fenofibrate 160 mg QD for 7 days	↑18%	↑ 11%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days	↓ 2%	↓0.2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	↑ 6%	↓ 7%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days	↑ 4%	↓ 9%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15	↑10%	↑15%
Grapefruit Juice	Pitavastatin 2 mg single dose on Day 3 + grapefruit juice	↑ 15%	↓ 12%

	for 4 days		
Itraconazole	Pitavastatin 4 mg single dose on Day 4 + itraconazole 200 mg daily for 5 days	↓ 23%	↓ 22%

*Data presented as x-fold change represent the ratio between co-administration and pitavastatin alone (i.e., 1-fold = no change). Data presented as % change represent % difference relative to pitavastatin alone (i.e., 0% = no change).
† Considered clinically significant *[see DOSAGE AND ADMINISTRATION (2) and DRUG INTERACTIONS (7)]*
BID = twice daily; QD = once daily; LA = Long Acting

Table 3. Effect of Pitavastatin Co-Administration on Systemic Exposure to Other Drugs

Co-administered drug	Dose regimen		Change in AUC*	Change in C_{max} *
Atazanavir	Pitavastatin 4 mg QD + atazanavir 300 mg daily for 5 days		↑ 6%	↑ 13%
Darunavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 3%	↑ 6%
Lopinavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 9%	↓ 7%
Ritonavir	Pitavastatin 4 mg QD on Days 1-5 and 20-24 + lopinavir/ritonavir 400 mg/100 mg BID on Days 9 – 24		↓ 11%	↓ 11%
Ritonavir	Pitavastatin 4mg QD on Days 1-5 and 12-16 + darunavir/ritonavir 800mg/100 mg QD on Days 6-16		↑ 8%	↑ 2%
Enalapril	Pitavastatin 4 mg QD + enalapril 20 mg daily for 5 days	Enalapril	↑ 12%	↑ 12%
		Enalaprilat	↓ 1%	↓ 1%
Warfarin	Individualized maintenance dose of warfarin (2 -7 mg) for 8 days + pitavastatin 4 mg QD for 9 days	R-warfarin	↑ 7%	↑ 3%
		S-warfarin	↑ 6%	↑ 3%
Ezetimibe	Pitavastatin 2 mg QD + ezetimibe 10 mg for 7 days		↑ 9%	↑ 2%
Digoxin	Pitavastatin 4 mg QD + digoxin 0.25 mg for 7 days		↓ 3%	↓ 4%
Diltiazem LA	Pitavastatin 4 mg QD on Days 1-5 and 11-15 and diltiazem LA 240 mg on Days 6-15		↓ 2%	↓ 7%
Rifampin	Pitavastatin 4 mg QD + rifampin 600 mg QD for 5 days		↓ 15%	↓ 18%

* Data presented as % change represent % difference relative to the investigated drug alone (i.e., 0% = no change).
BID = twice daily; QD = once daily; LA = Long Acting

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Pitavastatin inhibits cholesterol synthesis in the liver by competitively inhibiting HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate. On August 3, 2009, LIVALO® (pitavastatin) tablet

(calcium salt; strengths of 1 mg, 2 mg, and 4 mg, equivalent to 1 mg, 2 mg, and 4 mg pitavastatin, respectively) from Kowa Pharmaceuticals America, Inc. was approved by the FDA under NDA 022363 for the treatment of primary hyperlipidemia and mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol.

On October 21, 2016, Lupin Limited submitted this NDA application for pitavastatin tablet (sodium salt; strengths of 1 mg, 2 mg, and 4 mg, equivalent to 1 mg, 2 mg, and 4 mg pitavastatin, respectively) via 505(b)(2) pathway using LIVALO® (pitavastatin) tablet as reference product, proposing the same dosage, route of administration, and indications. There is no previous communication between Lupin Limited and the Agency before the NDA submission.

3.2 General Pharmacology and Pharmacokinetic Characteristics of Pitavastatin

Pitavastatin sodium drug substance is white to pale yellow powder. Pitavastatin sodium is freely soluble in water with pH dependent solubility and slightly soluble in N, N-Dimethylformamide. Its chemical name is sodium (3R, 5S, E)-7-(2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl)-3,5-dihydroxyhept-6-enoate and its molecular formula is $C_{25}H_{23}FNO_4Na$ (molecular weight 443.15) (Figure 1).

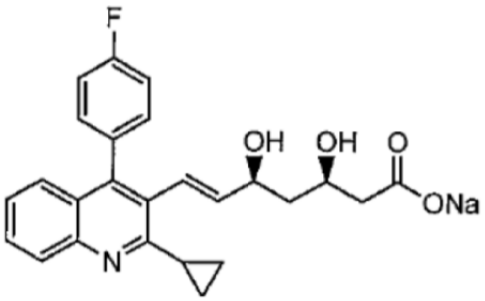


Figure 1. Structure of Pitavastatin Sodium

The relevant information about general pharmacology and pharmacokinetics of pitavastatin from the labeling of LIVALO® (pitavastatin) Tablets is summarized as below.

Mechanism of Action

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases levels of very low density lipoproteins.

Pharmacokinetics

Absorption: Pitavastatin peak plasma concentrations are achieved about 1 hour after oral administration. Both Cmax and AUC0-inf increased in an approximately dose-proportional manner for single LIVALO doses from 1 to 24 mg once daily. The absolute bioavailability of

pitavastatin oral solution is 51%. Administration of LIVALO with a high fat meal (50% fat content) decreases pitavastatin Cmax by 43% but does not significantly reduce pitavastatin AUC. The Cmax and AUC of pitavastatin did not differ following evening or morning drug administration. In healthy volunteers receiving 4 mg pitavastatin, the percent change from baseline for LDL-C following evening dosing was slightly greater than that following morning dosing. Pitavastatin was absorbed in the small intestine but very little in the colon.

Distribution: Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Association of pitavastatin and/or its metabolites with the blood cells is minimal.

Metabolism: Pitavastatin is marginally metabolized by CYP2C9 and to a lesser extent by CYP2C8. The major metabolite in human plasma is the lactone which is formed via an ester-type pitavastatin glucuronide conjugate by uridine 5'-diphosphate (UDP) glucuronosyltransferase (UGT1A3 and UGT2B7).

Excretion: A mean of 15% of radioactivity of orally administered, single 32 mg ^{14}C-labeled pitavastatin dose was excreted in urine, whereas a mean of 79% of the dose was excreted in feces within 7 days. The mean plasma elimination half-life is approximately 12 hours.

3.3 Clinical Pharmacology Review Questions

3.3.1 What is the relative bioavailability between 4 mg pitavastatin tablet (sodium salt) and 4mg LIVALO® (pitavastatin) tablet (calcium salt)?

Two studies, Study LBC-ARL/16/056 and Study LBC-ARL/16/057, were conducted to demonstrate the BE between the test product (4 mg pitavastatin tablet (sodium salt), equivalent to 4 mg pitavastatin) and the reference product (4mg LIVALO® (pitavastatin) tablet (calcium salt), equivalent to 4 mg pitavastatin) under fasting and fed conditions, respectively. Results indicate the 4 mg pitavastatin tablet is bioequivalent to 4mg LIVALO® (pitavastatin) tablet under both fasting and fed conditions.

The facility for both clinical studies including the analytical sites was requested to be inspected. The Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection since the requested inspection site was classified as No Action Indicated (NAI) based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 05/23/2017.

Fasting BE Study LBC-ARL/16/056

This is a randomized, open label, balanced, two treatment, two-period, two-sequence, single dose, crossover (10-day washout period) study in healthy male and female adults under fasting condition. Eligible subjects were randomized to receive single oral dose (1 x 4 mg tablet) of either test (T) or reference product (R) in each study period with 240 ± 2 mL of water at ambient temperature under fasting condition (at least 10.50-hour fasting prior to drug administration).

Blood samples were collected at pre-dose, 0.17, 0.33, 0.50, 0.75, 1, 1.25, 1.50, 2, 2.50, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose in each study period.

A total of 36 subjects were enrolled in the study and dosed in both periods. 35 subjects completed the study and were included in PK analysis. One subject was withdrawn from the study due to adverse event after dosing of period-II. PK results indicate that the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf of pitavastatin are all well within 80-125%, suggesting the bioequivalence between 4 mg pitavastatin tablet and 4mg LIVALO® (pitavastatin) tablet under fasting condition (Figure 2 and Table 1). The median Tmax of pitavastatin is 0.75 hour for both products with the ranges of 0.50-2.00 hours for the test and 0.33-1.25 hours for the reference product, respectively. The mean elimination half-life (T1/2) of pitavastatin is 12.12 hours (33.8% CV) for the test product and 12.20 hours (27.3% CV) for the reference product.

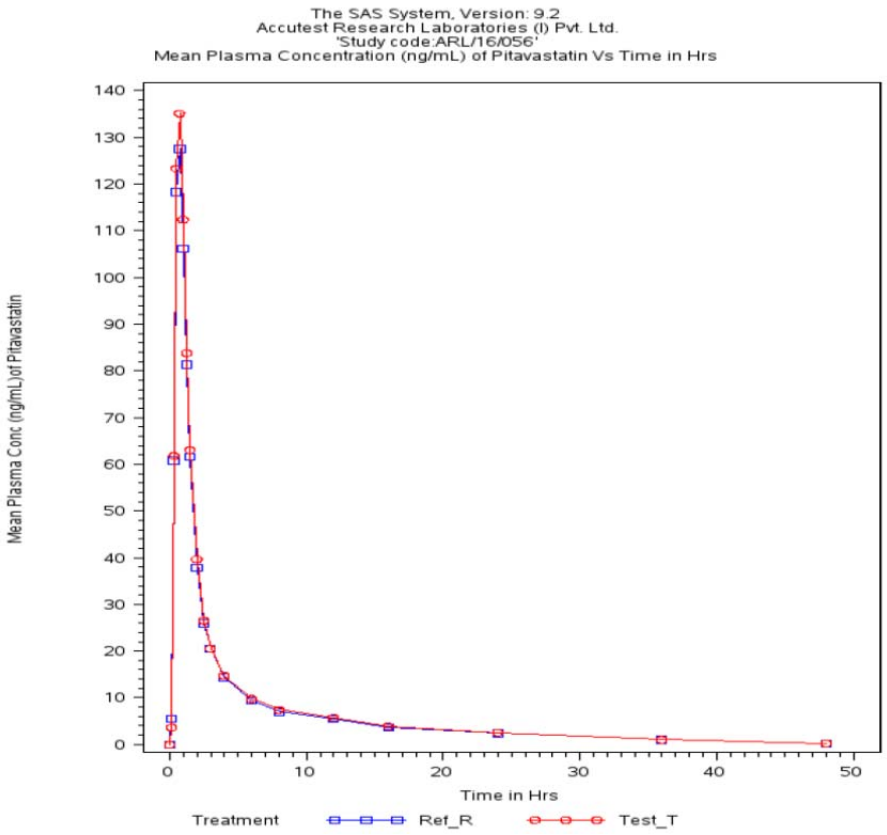


Figure 2. Mean plasma concentration-time profiles for pitavastatin following single oral administration of 4 mg pitavastatin tablet (sodium salt) and 4mg LIVALO® (pitavastatin) tablet (calcium salt) under fasting condition
(Source: Study LBC-ARL/16/056 CSR, Page 59 of 64)

Table 1. Bioequivalent analysis of pitavastatin following single oral administration of 4 mg pitavastatin tablet (sodium salt) and 4mg LIVALO® (pitavastatin) tablet (calcium salt) under fasting condition (N=35)

Parameters	Geometric Mean		% GMR (T/R)	90% CI of GMR
	Test (T)	Reference (R)		
Cmax (ng/mL)	131.4	127.8	102.8	(95.7, 110.3)
AUC0-t (h*ng/mL)	294.06	280.06	105.0	(100.7, 109.5)
AUC0-inf (h*ng/mL)	319.08	305.39	104.5	(100.4, 108.7)

(Reviewer's analysis)

Fed BE Study LBC-ARL/16/057

The BE study design under fed condition is identical to the BE study under fasting condition except that the single oral dose (1 x 4 mg tablet) of either test (T) or reference product (R) was administered 30 min after the high-fat and high-calorie breakfast (Table 2). Blood samples were collected at pre-dose, 0.50, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours post dose in each study period.

Table 2. High-fat and high-calorie breakfast give at 30 minutes before dosing

Food-item	Amount	CHO (g)	Protein (g)	Fat (g)	Energy (Kcal)
01) Whole Milk	240ml	11.3	7.9	8.9	157
02) Aloo Tiki	2 no (~70g)	26.9	2.7	11.3	220
		Breadcrumbs for binding & Spices to taste only			
03) Chicken fry	50g	1.29	14.57	5.86	116
04) Bread Butter (2 slices of Bread with butter)	45g	26	3.9	0.4	123
	20g	0	0	16.2	146
05) Egg Fry (2 eggs fried in butter)	~90g	0	13.3	17.4	210
Total		**65.5**	**42.37**	**60.06**	**972**
Calories(Kcal)		**262**	**169**	**541**	**NA**
Percent		**26.95**	**17.44**	**55.61**	**NA**

Abbreviation:-CHO: carbohydrates, g: grams, ml: milliliter, Kcal: Kilo calories, ~: approximate, no: number

(Source: Study LBC-ARL/16/057 CSR Appendix-16.1.1, Page 44 of 66)

A total of 36 subjects were enrolled in the study and 32 of them completed the study and were included in PK analysis. One subject was dropped-out from the study prior to dosing of period-I due to personal reason. Two subjects were withdrawn from the study after dosing in Period-I and Period-II, respectively, due to related moderate adverse events, including skin rash and nausea with vomiting.

PK results indicate that the 90% CIs of the geometric mean ratios of Cmax, AUC0-t, and AUC0-inf of pitavastatin are all well within 80-125%, suggesting the BE between 4 mg pitavastatin tablet and 4mg LIVALO® (pitavastatin) tablet under fed condition (Figure 3 and Table 3). The median Tmax of pitavastatin is 1.25 hours (range 0.75-4.00 hours) for the test product and 1.50 hours (range 0.50-2.00 hours) for the reference product. The mean elimination half-life (T1/2) of pitavastatin is 11.19 hours (34.9% CV) for the test product and 12.76 hours (46.0% CV) for the reference product.

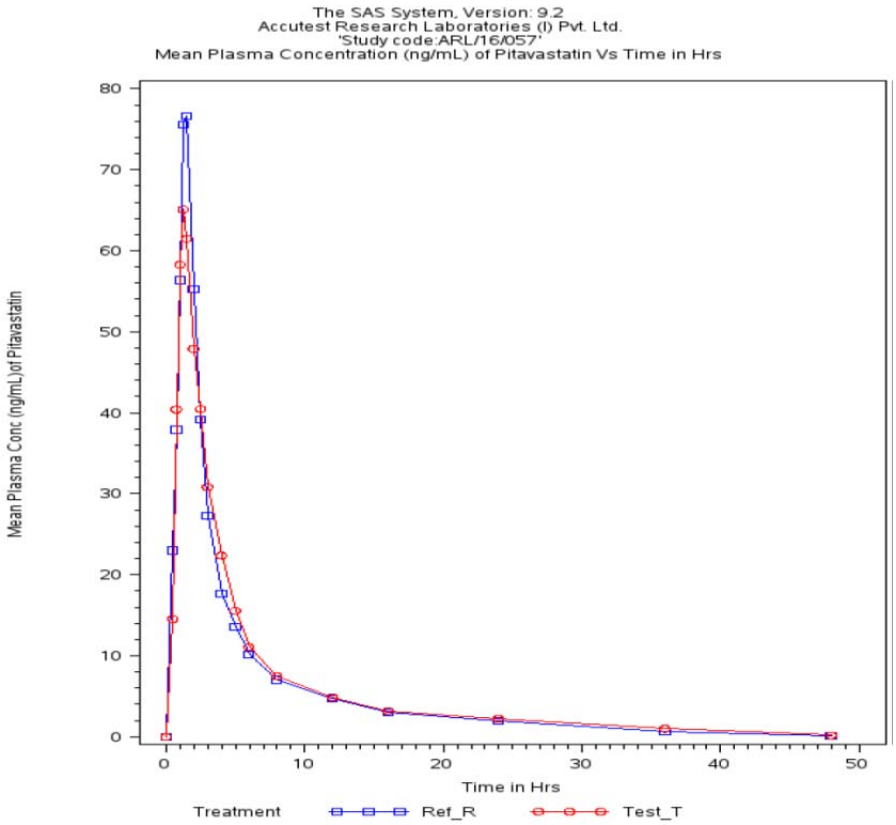


Figure 3. Mean plasma concentration-time profiles for pitavastatin following single oral administration of 4 mg pitavastatin tablet (sodium salt) and 4mg LIVALO® (pitavastatin) tablet (calcium salt) under fed condition
(Source: Study LBC-ARL/16/057 CSR, Page 60 of 66)

Table 3. Bioequivalent analysis of pitavastatin following single oral administration of 4 mg pitavastatin tablet (sodium salt) and 4mg LIVALO® (pitavastatin) tablet (calcium salt) under fed condition (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)

(Reviewer's analysis)

3.3.2 What is the formulation for the to-be-marketed pitavastatin tablet (sodium salt)?

The to-be-marketed formulation of pitavastatin tablet (sodium salt) was used in both BE studies (Table 4).

Table 4. Qualitative and Quantitative Composition of the Pitavastatin Tablet (sodium salt) Drug Product

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

(Source: Quality Overall Summary, Page 12 of 254)

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Determinations of pitavastatin in human plasma from Studies ARL/16/056 and ARL/16/057 were performed using fully validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays. The key descriptive parameters for the bioanalytical assay were summarized in Table 5.

The bioanalytical facility has been requested to be inspected. The OSIS recommends accepting data without an on-site inspection since the requested inspection site was classified as NAI based on recent inspections. For more detailed information, refer to the OSIS memorandum dated 05/23/2017.

Table 5. Summary of key descriptive parameters for pitavastatin bioanalytical assay used in Studies ARL/16/056 and ARL/16/057

Analyte	Pitavastatin
Analytical matrix	Human Plasma
Type of extraction	Solid phase extraction
Method of detection	SPE, LC-MS/MS
Internal standard	Pitavastatin-D4
Validated range	1.001 ng/mL to 200.172 ng/mL Pitavastatin
LLOQ	1.001 ng/mL
QC levels	LLQC: 1.003 ng/mL LQC: 2.999 ng/mL MQC: 70.212 ng/mL HQC: 150.454 ng/mL
Calibration model	Linear regression weighted
Weighting factor	1/X*X
Accuracy	Inter-day: 96.06%-104.94% for all QC levels Intra-day: 93.79%-104.64% for all QC levels
Precision	Inter-day: 1.68%-6.09% for all QC levels

	Intra-day: 0.69%-2.93% for all QC levels
Matrix effect	% Precision at LOC level: 1.62%
Bench top stability **(6 hours at RT)**	Accuracy: 96.64% at LOC and 101.37% at HQC Precision: 1.05% at LOC and 1.35% at HQC
Freeze thaw stability **(-70°C ±10°C, 5 FT cycles)**	Accuracy: 97.21% at LOC and 104.34% at HQC Precision: 2.09% at LOC and 2.12% at HQC
Autosampler stability **(55 Hrs at 10°C)**	Accuracy: 97.12% at LOC and 105.88% at HQC Precision: 3.32% at LOC and 1.79% at HQC
Stock solution stability	RT 22 hours: 0.80% prevision and 0.52% difference* 2-8 °C 10 Days: 0.53% prevision and -0.39% difference*
Working solution stability	RT 22 hours: 0.80% prevision and -0.87% difference* 2-8 °C 10 Days: 1.16% prevision and -0.82% difference*
Long-term stability **(-70°C ±10°C for 281 days)**	% Difference*: 5.03% for LQC and -1.19% for HQC
Dilution integrity **(from 341.309 ng/mL pitavastatin)**	2 times dilution: 4.52% prevision and 105.03% accuracy 4 times dilution: 2.80% prevision and 100.91% accuracy
Reinjection reproducibility	Precision: 1.05%-1.94% for all QC levels Accuracy: 99.41%-104.69% for all QC levels
Sample storage conditions	-70°C ±10°C
Duration of sample analysis	Within 42 days for Study ARL/16/056 Within 50 days for Study ARL/16/057

RT: room temperature; LLOQ: Lower limit of quantification; LLQC: Lower limit of quantification quality control; LQC: Lower quality control; MQC: Middle Quality Control; HQC: Higher quality control

*Difference should be within ±10% when compared with freshly prepared stock solution

(Source: Summarized from Bioanalytical Method Validation Report ARL/REP/MI/193PPL/01 and Bioanalytical Reports for Studies ARL/16/056 and ARL/16/057)

4.2 Study Synopsis

Fasting BE Study LBC-ARL/16/056

Name of the Sponsor: Lupin Limited, India	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of the Finished Product: PITAVASTATIN TABLETS 4 MG		
Name of Active Ingredient: PITAVASTATIN		
Title of the study: A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Pitavastatin Tablets 4 mg of Lupin Limited, India with Livalo® (Pitavastatin) Tablets 4 mg of Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA in Normal, Healthy, Adult, Human Subjects under Fasting Condition.		
Investigators and other important participants in the study:		
Dr. Alpesh Patel, Principal Investigator (b) (4)	Dr. Paresh Mistry, Head-Quality Assurance (For Clinical) (b) (4)	
Study centre(s): ***Clinical Facility and Statistical (For Randomization) Facility:*** Accutest Research Laboratories (I) Pvt. Ltd. (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA. Tel.: +91 79- 4023 1600; Fax: +91 79-40029317 ***Bio-analytical Facility:*** (b) (4)		

Statistical Facility:

Accutest Research Laboratories (I) Pvt. Ltd.

A-77, M.I.D.C, TTC Industrial Area, Khairne, Navi Mumbai –400 709, Maharashtra, INDIA.

Tel: + 91 22 2778 0718/19/21, Fax: + 91 22 2778 0720

Publication (reference): None

Study period:

Period-I: 19 April 2016 - 22 April 2016

Period-II: 28 April 2016- 01 May 2016

Clinical Completion Date: 04 May 2016

Objectives: 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 fasting conditions.

Secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).

Methodology: This was randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover study in normal, healthy, adult, male and female human subjects under fasting condition. Subjects underwent screening evaluations to determine eligibility within 21 days prior to dosing of Period-I. The subjects were confined within the facility for at least 10.50 hours prior to drug administration and until 24.00 hours post dose in each study period. Subjects were randomized to receive single oral dose (1 x 4 mg tablet) of either test (T) or reference product (R) in each study period with 240 ± 2 mL of water at ambient temperature under fasting condition. Blood samples were drawn from pre-dose (collected within 01.00 hour prior to dosing) and up to 48.00 hours post dose in each study period. Analysis of Plasma concentrations of Pitavastatin was done by a validated LC-MS/MS analytical method.

Note: All activities related to handling of investigational medicinal products, dosing, blood sample collection, sample handling, processing and sample analysis were carried out under sodium vapour light.

Number of subjects (planned and analyzed):

Total no. of subjects planned =36 (28 Male & 08 Female)

Total no. of subjects enrolled = 36

Total no. of subjects dosed in Period I = 36

Total no. of subjects dosed in Period II = 36

Total no. of subjects completed the study = 35 (27 Male & 08 Female)

No. of subjects withdrawn = 01

No. of subjects dropped-out = None

No. of subjects analysed in bioanalytical facility = 36

No. of subjects included in Pharmacokinetic and Statistical analysis as per protocol =35

Note: *Subject no. 09 was withdrawn from the study due to adverse event after dosing of period-II.*

Diagnosis and main criteria for inclusion: Male and female human subjects having age in the range of 18-45 years (both inclusive), BMI between 18.5-24.9 kg/m^2 (extreme included), who were healthy as determined by clinical history, physical examinations, clinical laboratory assessments, vital sign measurements, 12-lead ECG, chest X-ray (if not done within 6 months prior to the study) and who met all other inclusion criteria were enrolled.

	Test product (T)	**Reference product (R)**
Name of IMP/	PITAVASTATIN TABLETS	Livalo® (Pitavastatin) tablets
Brand Name:	4 MG	4 mg
	(Name of IMP)	(Brand Name)
Dose:	1 x 4 mg Tablet	1 x 4 mg Tablet
Mode of administration:	Oral	Oral
Batch No./ Lot No.:	M590478 (Batch No.)	3121762 (Lot No.)

Duration of treatment: Single oral dose (1 x 4 mg Tablet) of either test product (T) or reference product (R) in each study period over 12 days.

Criteria for evaluation:

Efficacy:

Bioequivalence Criteria: The 90% confidence interval of geometric mean ratio of $C_{max,}$ AUC_{0-t} and AUC_{0-inf} between test and reference product fall within the range of 80.00% to 125.00% for Pitavastatin.

Safety: Safety assessments were based on medical review of adverse events (AEs), SAEs, physical examination, recording of vital signs, 12 Lead ECG and clinical laboratory tests.

Statistical methods:

ANOVA was performed on ln transformed pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and AUC_{0-inf} at the α level of 0.05 & 90% confidence interval for the ratio of the geometric means for ln-transformed pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and AUC_{0-inf} were performed using SAS® Software (Version 9.2) for Pitavastatin.

SUMMARY – CONCLUSIONS:

BIOEQUIVALENCE RESULTS:

The data of 35 subjects were considered to perform Pharmacokinetic and Statistical analyses.

The 90% confidence intervals of ln-transformed parameters for Pitavastatin are summarized below:

Table 01: Geometric Means, Ratios and 90% Confidence Intervals for Pitavastatin (N=35)

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-inf}	319.23	304.90	104.7005	100.6894	108.8712
AUC_{0-t}	291.33	277.83	104.8606	100.3985	109.5211
C_{max}	131.42	127.85	102.7900	95.7497	110.3479

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.*

SAFETY RESULTS:

A single oral dose of [1 x 4 mg Tablet] PITAVASTATIN TABLETS 4 MG was well tolerated. One [(01)-Vomiting with mild burning pain in epigastrium] adverse event was reported during entire course of the study. The reported adverse event was moderate in severity, possibly related to the study medication and was resolved.

No any serious or significant adverse event was reported during the entire course of the study. Laboratory values, which were not found within provided normal reference range, were evaluated either clinically significant or not significant on the basis of clinical acceptable values. No clinically significant findings were observed during entire course of the study. The values which were clinically not significant were recorded in case report form.

CONCLUSION:

Based on the statistical analysis, it has been concluded that the Test Product (T): PITAVASTATIN TABLETS 4 MG manufactured by: LUPIN LTD, (b) (4) NAGPUR, INDIA, is bioequivalent with the Reference Product (R): Livalo® (Pitavastatin) tablets 4 mg manufactured by: Patheon, Inc. Cincinnati, OH 45237 USA or by Kowa Company Ltd Nagoya, 462-0024 Japan marketed by: Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA, under fasting condition.

Date of the report: 05 July 2016

Fed BE Study LBC-ARL/16/057

Name of the Sponsor: Lupin Limited, India	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of the Finished Product: PITAVASTATIN TABLETS 4 MG		
Name of Active Ingredient: PITAVASTATIN		
Title of the study: A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Pitavastatin Tablets 4 mg of Lupin Limited, India with Livalo® (Pitavastatin) Tablets 4 mg of Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA in Normal, Healthy, Adult, Human subjects under Fed Condition.		
Investigators and other important participants in the study:		
Dr. Alpesh Patel, Principal Investigator (b) (4)	Dr. Paresh Mistry, Head-Quality Assurance (For Clinical) (b) (4)	

Study centre(s):

Clinical Facility and Statistical (For Randomization) Facility:

Accutest Research Laboratories (I) Pvt. Ltd. (Unit-II)

Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev,

Ahmedabad -380059, INDIA.

Tel.: +91 79- 4023 1600; Fax: +91 79-40029317

Bioanalytical Facility:

(b) (4)

Statistical Facility:

Accutest Research Laboratories (I) Pvt. Ltd.

A-77, M.I.D.C, TTC Industrial Area, Khairne, Navi Mumbai –400 709, Maharashtra, INDIA.

Tel: + 91 22 2778 0718/19/21, Fax: + 91 22 2778 0720

Publication (reference): None
Study period: Period-I: 21 April 2016 - 24 April 2016 Period-II: 30 April 2016- 03 May 2016 Clinical Completion Date: 03 May 2016
Objectives: 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 fed conditions. Secondary objective was to monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).

Methodology: This was a randomized, open label, balanced, two treatment, two period, two sequence, single dose, crossover study in normal, healthy, adult, male and female human subjects under fed condition. Subjects underwent screening evaluations to determine eligibility within 21 days prior to dosing of Period-I. The subjects were confined within the facility for at least 10.50 hours prior to drug administration and until 24.00 hours post dose in each study period. Subjects were randomized to receive single oral dose (1 x 4 mg tablets) of either test (T) or reference product (R) in each study period with 240 ± 2 mL of water at ambient temperature after receiving the high-fat and high-calorie breakfast, which was started by subject exactly 30 min prior to drug administration. Blood samples were drawn from pre-dose (collected within 01.00 hour prior to dosing) and up to 48.00 hours post dose in each study period. Analysis of Plasma concentrations of Pitavastatin was done by a validated LC-MS/MS analytical method. *Note: All activities related to handling of investigational medicinal products, dosing, blood sample collection, sample handling, processing and sample analysis were carried out under sodium vapour light.*

Number of subjects (planned and analyzed):

Total no. of subjects planned =36 (34 Male & 02 Female)

Total no. of subjects enrolled = 36

Total no. of subjects dosed in Period I = 35 (33 Male & 02 Female)

Total no. of subjects dosed in Period II = 34 (32 Male & 02 Female)

Total no. of subjects completed the study = 32 (30 Male & 02 Female)

No. of subjects withdrawn = 03

No. of subjects dropped-out = 01

No. of subjects analysed in bioanalytical facility = 35

No. of subjects included in Pharmacokinetic and Statistical analysis as per protocol =32

Note: *Subject no.10 was dropped-out from the study prior to dosing of period-I due to personal reason. Subject no.18 was withdrawn from the study after dosing of period-I due to adverse event. Subject no.04 and 12 were withdrawn from the study after dosing of period-II due to adverse event.*

Diagnosis and main criteria for inclusion: Male and female human subjects having age in the range of 18-45 years (both inclusive), BMI between 18.5-24.9 kg/m^2 extremes included, who were healthy as determined by clinical history, physical examinations, clinical laboratory assessments, vital sign measurements, 12-lead ECG, chest X-ray (if not done within 6 months prior to the study) and who met all other inclusion criteria were enrolled.

	Test product (T)	**Reference product (R)**
Name of IMP/	PITAVASTATIN TABLETS	Livalo® (Pitavastatin) tablets
Brand Name:	4 MG	4 mg
	(Name of IMP)	(Brand Name)
Dose:	1 x 4 mg Tablet	1 x 4 mg Tablet
Mode of administration:	Oral	Oral
Batch No./ Lot No.:	M590478 (Batch No.)	3121762 (Lot No.)

Duration of treatment: Single oral dose (1 x 4 mg Tablet) of either test product (T) or reference product (R) in each study period over 12 days.

Criteria for evaluation:

Efficacy:

Bioequivalence Criteria: The 90% confidence interval of geometric mean ratio of $C_{max,}$ AUC_{0-t} and AUC_{0-inf} between test and reference product fall within the range of 80.00% to 125.00% for Pitavastatin.

Safety: Safety assessments were based on medical review of adverse events (AEs), SAEs, physical examination, recording of vital signs, 12 Lead ECG and clinical laboratory tests.

Statistical methods:

ANOVA was performed on ln transformed pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and AUC_{0-inf} at the α level of 0.05 & 90% confidence interval for the ratio of the geometric means for ln-transformed pharmacokinetic parameters $C_{max,}$ AUC_{0-t} and AUC_{0-inf} were performed using SAS® Software (Version 9.2) for Pitavastatin.

SUMMARY – CONCLUSIONS:

BIOEQUIVALENCE RESULTS:

The data of 32 subjects were considered to perform Pharmacokinetic and Statistical analyses.

The 90% confidence intervals of ln-transformed parameters for Pitavastatin are summarized below:

Table 01: Geometric Means, Ratios and 90% Confidence Intervals for Pitavastatin (N=32)

Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
AUC_{0-inf}	271.47	272.27	99.7090	94.7837	104.8903
AUC_{0-t}	247.70	244.58	101.2767	96.0345	106.8050
C_{max}	74.54	80.48	92.6175	85.3249	100.5334

**Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.*

SAFETY RESULTS:

A single oral dose of [1 x 4 mg Tablet] PITAVASTATIN TABLETS 4 MG was well tolerated. Total of three [(03) - Diarrhoea, Skin rash on both upper and lower extremities with itching and Nausea with vomiting] AEs were reported during entire course of the study. The reported AEs were moderate in severity, probably to possibly related to the study medication and they were resolved.

No any serious or significant adverse event was reported during the entire course of the study. Laboratory values, which were not found within provided normal reference range, were evaluated either clinically significant or not significant on the basis of clinical acceptable values. No clinically significant findings were observed during entire course of the study. The values which were clinically not significant were recorded in case report form.

CONCLUSION:

Based on the statistical analysis, it has been concluded that the Test Product (T): PITAVASTATIN TABLETS 4 MG manufactured by: LUPIN LTD, (b) (4) NAGPUR, INDIA, is bioequivalent with the Reference Product (R): Livalo® (Pitavastatin) tablets 4 mg manufactured by: Patheon, Inc. Cincinnati, OH 45237 USA or by Kowa Company Ltd Nagoya, 462-0024 Japan marketed by: Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA, under fed condition.

Date of the report: 20 July 2016

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

/s/

LEI HE
07/12/2017

JAYABHARATHI VAIDYANATHAN
07/12/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	209875	**SDN**	1
Applicant	Lupin Limited	**Submission Date**	10/21/2016
Generic Name	Pitavastatin sodium	**Brand Name**	NA
Drug Class	Statin		
Indications	This is a 505 (b)(2) NDA submission. The proposed indications are same as the reference product, LIVALO (pitavastatin) Tables (NDA 022363). • Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and to increase high-density lipoprotein cholesterol. • Limitations of use: o Do not exceed 4 mg once daily dosing of pitavastatin o The effect on cardiovascular morbidity and mortality has not been determined o Pitavastatin has not been studied in Fredrickson Type I, III, and V dyslipidemias.		
Dosage Regimen	This is a 505 (b)(2) NDA submission. The proposed dosage regimens are same as the reference product, LIVALO (pitavastatin) Tables (NDA 022363). • Pitavastatin tables can be taken with or without food, at any time of day. Dose Range: 1 mg to 4 mg once daily • Primary hyperlipidemia and mixed dyslipidemia: Starting dose 2 mg. When lowering of LDL-C is insufficient, the dosage may be increased to a maximum of 4 mg per day. • Moderate and severe renal impairment as well as end-stage renal disease on hemodialysis: Starting dose of 1 mg once daily and maximum dose of 2 mg once daily		
Dosage Form	Tablets	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	Metabolism and Endocrinology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Lei He, PhD	Jayabharathi Vaidyanathan, PhD
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/20/2016	**74-Day Letter Date**	1/3/2017
Review Due Date	7/17/2017	**PDUFA Goal Date**	8/21/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

To support this 505 (b)(2) NDA submission, Lupin conducted two bioequivalence (BE) studies, Studies LBC-ARL/16/056 and LBC- ARL/16/057 in healthy subjects under fasting and fed conditions, respectively, comparing pitavastatin tablets (4 mg) with the reference product, Livalo (pitavastatin tablets, 4 mg). No other clinical pharmacology studies have been conducted. These two BE studies were conducted at a single clinical laboratory and the pharmacokinetic assay were conducted in one bioanalytical facility. The results of these two BE studies serve as the basis to support this 505(b)(2) NDA submission. Therefore, we request that both the clinical site and analytical site be inspected for this submission.

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☑ Other			Bioanalytical reports: 1) Method validation report (ARL/REP/MI/193PPL/01): simultaneous estimation of pitavastatin and its metabolite pitavastatin lactone in human plasma 2) Bioanalytical report for Study LBC- ARL/16/056 3) Bioanalytical report for Study LBC- ARL/16/057
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		Study LBC- ARL/16/056 (Fasting BE study) Study LBC- ARL/16/057 (Fed BE study)
	☐ Multiple Dose		
Patients	☐ Single Dose		

☐ Multiple Dose			
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	3	**In Vivo**	2
Total Number of Studies to be Reviewed				

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo
See Attachment: Presentation slides in filing meeting.

U.S. FOOD & DRUG ADMINISTRATION

NDA 209875 (505(b)(2))

Pitavastatin Tablets (1, 2, 4 mg tables, oral)

Lupin Limited

Filing Meeting

Clinical Pharmacology

Lei He, Jayabharathi Vaidyanathan

12/05/2016

Clinical Pharmacology Summary

- Application is fileable from a clinical pharmacology perspective.
- Key review questions
  - Is the proposed piavastatin tablets BE to Livalo under fasting and fed conditions?
  - Are the bioanalytical methods validated?
- Topline results
  - BE was demonstrated between the proposed pitavastatin tablets 4 mg and RLD 4 mg in healthy subjects under fasting and fed conditions.
  - The bioanalytical methods were fully validated.

2

Background

	NDA 209875 (505(b)2)	NDA022363 (RLD) (approved 08/03/2009)
Sponsor	Lupin Limited	KOWA KO
Drug product	Pitavastatin Tablets	LIVALO® (pitavastatin) Tablets
Drug substance	Pitavastatin **Sodium**	Pitavastatin **Calcium**
Active moiety	Pitavastatin	
Strengths	1, 2, 4 mg	
Route of administration	Oral	
Proposed indications	Patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy Limitations of use: • Do not exceed 4 mg once daily dosing of pitavastatin • The effect on cardiovascular morbidity and mortality has not been determined • Has not been studied in Fredrickson Type I, III, and V dyslipidemias.	

Bioequivalence Studies

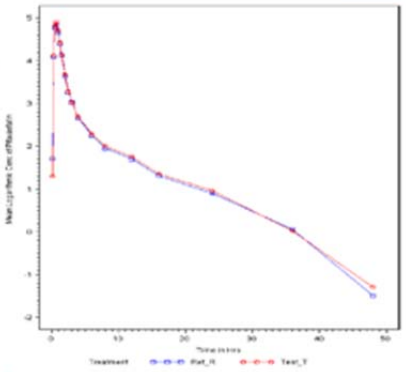
Study	Study design	Study population	Test product	Results
Fasting BE study (LBC-ARL/16/056)	R, OL, balanced, 2-Treatment, 2-P, SD, CO, 10-day washout	36 HS (28M/8F, 35 completed)	Pitavastatin Tablets or RLD, 4 mg	BE demonstrated
Fed BE study (LBC-ARL/16/057)	R, OL, balanced, 2-Treatment, 2-P, SD, CO, 10-day washout	36 HS (34M/2F, 32 completed)	Pitavastatin Tablets or RLD, 4 mg	BE demonstrated

The proposed commercial formulation was used in both studies.

***In vitro* Comparison Dissolution Study:** Lupin's Pitavastatin Tablets, 1 mg and 2 mg are proportionally similar in both active and inactive ingredients to that of the Pitavastatin Tablets, 4 mg. Therefore, biowaiver is requested for Pitavastatin Tablets, 1 mg and 2 mg.

Fasting BE Study

- R, OL, balanced, 2-treatment, 2-P, SD, CO, 10-day washout, in 36 HS (28M/8F, 35 completed)
- Dosing: Fasting condition, single dose, pitavastatin tablets or RLD, 4 mg, oral



Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
$AUC_{0\text{-}inf}$	319.23	304.90	104.7005	100.6894	108.8712
$AUC_{0\text{-}t}$	291.33	277.83	104.8606	100.3985	109.5211
C_{max}	131.42	127.85	102.7900	95.7497	110.3479

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

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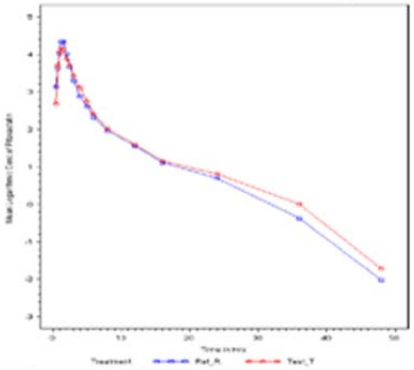
Fed BE Study

- R, OL, balanced, 2-treatment, 2-P, SD, CO, 10-day washout, in 36 HS (34M/2F, 32 completed)
- Dosing: Fed condition, single dose, pitavastatin tablets or RLD, 4 mg, oral



Parameters	*Geometric mean		% Ratio	90% Confidence Interval for ln-transformed data	
	Test (T)	Reference (R)	T/R	Lower Limit	Upper Limit
$AUC_{0\text{-}inf}$	271.47	272.27	99.7090	94.7837	104.8903
$AUC_{0\text{-}t}$	247.70	244.58	101.2767	96.0345	106.8050
C_{max}	74.54	80.48	92.6175	85.3249	100.5334

*Geometric mean was taken as the antilog (exponential) of the Least square mean of the ln-transformed data.

Summary

- Application is fileable
- Mid-cycle deliverables
  - Any approvability issues
  - Confirm PK results
- OSI inspection requested

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/s/

LEI HE
12/06/2016

JAYABHARATHI VAIDYANATHAN
12/06/2016