CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208379Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208-379 Serials 000; 001; 002; 007
Submission Dates	March 31, 2015; June 12, 2015; July 6, 2015; October 2, 2015
Brand Name	ZYPITAMAG
Generic Name	Pitavastatin magnesium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Zydus Pharmaceuticals
Formulation; Strength	Immediate release tablets; 1, 2, and 4 mg
Relevant IND	117,674
Indication	Adjunct therapy to diet to reduce elevated lipid concentrations

Table of Contents **Page**

1 Executive Summary

The sponsor seeks approval of 1, 2, and 4 mg pitavastatin tablets (magnesium salt) as an adjunct therapy to reduce elevated lipid concentrations via the regulatory 505(b)(2) pathway. The 1, 2, and 4 mg pitavastatin tablets (calcium salt; LIVALO) have the indication to treat hyperlipidemia (NDA 22-363 approval on August 3, 2009).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 208-379's Clinical Pharmacology data submitted on March 31, 2015, June 12, 2015, July 6, 2015, and October 2, 2015. The data are acceptable to support approval provided that a mutual agreement for the label language can be reached between the sponsor and the Food and Drug Administration.

1.2 Post Marketing Requirement
None.

1.3 Summary of Important Clinical Pharmacology Findings
The sponsor submitted the results of 2 clinical pharmacology studies (BA1386248 and BA1386249) to support NDA 208-379. Study BA1386248 assessed the relative bioavailability between 4 mg pitavastatin tablet (magnesium salt) and 4 mg pitavastatin tablet (calcium salt). Study BA1386249 assessed the food effect on the bioavailability of 4 mg pitavastatin tablet (magnesium salt). The sponsor requested a biowaiver for the 1 and 2 mg pitavastatin tablets (magnesium salt). See Biopharmaceutics reviewer's review for the request of biowaiver.

The 4 mg pitavastatin tablet (magnesium salt) is bioequivalent to the 4 mg pitavastatin tablet (calcium salt; LIVALO) under fasting condition. A high fat meal decreases pitavastatin C_{max} and AUC by 38.6 and about 5%, respectively, upon oral administration of a 4 mg pitavastatin tablet (magnesium salt). This decrease in pitavastatin AUC is not significant.

The pitavastatin tablets (magnesium salt) tested in Study BA1386248 are the same as the to-be-marketed pitavastatin tablets (magnesium salt). The size of biobatch for 4 mg pitavastatin tablets (magnesium salt) used in Study BA1386248 is (b) (4) tablets, which is larger than (b) (4) tablets and thus acceptable for bioequivalence assessment. The sponsor used the US-manufactured 4 mg LIVALO tablets to conduct Study BA1386248. The Orange Book lists 4 mg LIVALO tablet as the reference listed drug. The sponsor claimed that they kept all remaining test drug supplies as retention samples per the USFDA requirements.

Overall, Clinical Pharmacology recommends the approval of NDA 208-379.

2 Question-Based Review

2.1 Background

The sponsor is developing 1, 2, and 4 mg pitavastatin tablets (magnesium salt) to treat hypercholesterolemia via the regulatory 505(b)(2) pathway. The innovator 1, 2, and 4 mg pitavasatin tablets (calcium salt) have the indication to treat hypercholesterolemia. Refer to the clinical pharmacology review of pitavastatin tablets (calcium salt; NDA 22-363) dated July 17, 2009 in DARRTS.

The Division of Metabolism and Endocrinology Products responded to the sponsor's question via a preIND 117,674 correspondence on April 15, 2013:

> **Question 1**: ***Do we need to provide any other safety and/or efficacy study other than the BE study at the time of 505b2 application submission? If yes, then please suggest specific study and design.***
> The most sensitive design to determine equivalence of rate and extent of exposure is the single dose fasting study design. However, the effect of food on your new salt formulation should also be ascertained. Therefore we recommend the following two studies for your 505(b)(2) application: (a) a single-dose fasting bioequivalence study comparing pitavastatin magnesium 4 mg (test) against pitavastatin calcium 4 mg (reference), and (b) a single-dose food-effect study comparing pitavastatin magnesium 4 mg under fasting (reference) and fed (test) conditions. Additional clinical trials beyond these two studies would not be required provided adequate data are submitted to bridge your product, pitavastatin magnesium, and the listed drug, Livalo. Please modify protocol# BA1286505 accordingly. Guidance for designing a food-effect study may be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf.

See clinical pharmacology memo for IND 117,674 dated September 13, 2013 in DARRTS.

The sponsor conducted the following 2 studies to support NDA 208-379:

- Study BA1386248 assessed the relative bioavailability between 4 mg pitavastatin tablet (magnesium salt) and 4 mg pitavastatin tablet (calcium salt) under fasting
- Study BA1386249 assessed the food effect on the bioavailability of pitavastatin tablet (magnesium salt).

See clinical pharmacology review for IND 117,674 dated July 3, 2013 in DARRTS.

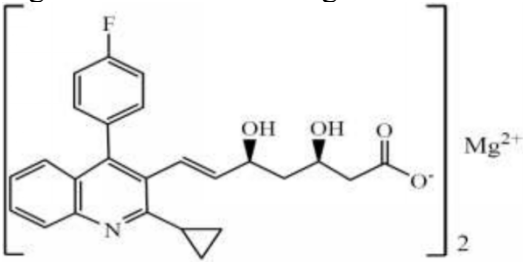
Besides pitavastatin calcium's product label, the following publication details pitavastatin's clinical pharmacology:

- Duggan ST. Pitavastatin: a review of its use in the management of hypercholesterolaemia or mixed dyslipidaemia. *Drugs* 2012;72:565-84.

2.2 General Attributes

2.2.1 What are pitavastatin magnesium's key physicochemical properties?

Figure 1. Pitavastatin magnesium's molecular structure.



Source: Module 3.2.S.1.2

Figure 1 shows the chemical structure of pitavastatin magnesium, which has a molecular weight of 865.21 and empirical formula of $C_{50}H_{46}MgF_2N_2O_8$.

2.2.2 How do the physicochemical properties of pitavastatin magnesium compare with those of pitavastatin calcium?

Table 1 compares the physicochemical properties between pitavastatin magnesium and pitavastatin calcium.

Table 1. Physicochemical properties of pitavastatin magnesium and pitavastatin calcium.

Property	Pitavastatin Magnesium	Pitavastatin Calcium
Appearance	White to off white powder	White to off white powder
pH (1% w/v aqueous solution)	7.3	7.1
pK_a	5.31	5.31
Partition Coefficient	0.08	0.08
Solubility, mg/mL		
In water	1.66	0.67
In 0.1 N HCl	1.27	0.60
In pH 4.5 acetate buffer	1.19	0.56
In pH 6.8 phosphate buffer	2.61	3.2

Source: Modified from Module 3.2.S.1.3 General Properties, Page 2/2

2.2.3 What is the formulation for the to-be-marketed pitavastatin tablet (magnesium salt)?

Table 2 below details the formulation of the to-be-marketed immediate release pitavastatin tablets (magnesium salt).

Table 2. To-be-marketed pitavastatin tablets (magnesium salt)'s formulation.

Sr. No.	Name of Ingredient	Quantity / Unit (mg)			%w/w#	Function
		1 mg	2 mg	4 mg		
						(b) (4)
1	Pitavastatin Magnesium^	1.026	2.053	4.106	1.25	Active Ingredient
2	Lactose Monohydrate, NF				(b) (4)	(b) (4)
3	Crospovidone, NF (b) (4)					
4	Hypromellose, USP (b) (4)					
5	Sodium Carbonate, NF (Anhydrous (b) (4)					
6	Calcium Carbonate, NF (b) (4)					
	(b) (4)					
	(b) (4)					
8	Crospovidone, NF (b) (4)				(b) (4	
9	Magnesium Stearate, NF					
					(b) (4)	
Total		**82.000**	**164.000**	**328.000**	**100.00**	-

^1.026 mg, 2.053 mg and 4.106 mg of pitavastatin Mg is equivalent to 1mg, 2mg and 4mg of pitavastatin, respectively.
*Does not remain in final product, except in traces
#Quantity % w/w is calculated with respect to coated tablet weight
q.s.: Quantity Sufficient
Source: Module 3.2.P.1 Page 5/12

2.3 General Clinical Pharmacology

2.3.1 What are pitavastatin's clinical pharmacokinetic (PK) characteristics*?

The following is extracted from the Clinical Pharmacology review of pitavastatin tablet (calcium salt) *http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022363s000_ClinPharmR_P1.pdf.

Absorption
Upon oral administration of a single 4 mg pitavastatin tablet, the mean pitavastatin C_{max} , $AUC_{0\text{-}inf}$, and t_{max} (median) are 82 ng/mL, 209 ng·h/mL, and 0.75 hour, respectively. Pitavastatin is well absorbed in the proximal jejunum and distal jejunum/proximal ileum. Geometric mean pitavastatin absolute oral bioavailability of an oral solution is 51%. A high fat meal decreases pitavastatin C_{max} and AUC 43.1 and 11%, respectively, but the decrease in pitavastatin AUC is not significant. Pitavastatin pharmacokinetics (PK) is approximately dose-proportional for both oral single and multiple doses from 1 – 24 mg. Pitavastatin $AUC_{0\text{-}24}$ at steady state is 1.5 times that after a single dose.

Distribution
The mean pitavastatin volume of distribution is 211.4 L. Pitavastatin is 99.5 – 99.6% plasma protein bound. Pitavastatin primarily binds to serum albumin but also binds to α_1-acid glycoprotein. Pitavastatin lactone is 98.95 – 99.33% plasma protein bound. Association of pitavastatin and/or its metabolites with blood cells is minimal.

Metabolism
UDP-glucuronosyl transferase (UGT) 1A3 and 2B7 primarily metabolize pitavastatin to pitavastatin glucuronide, which in turn forms pitavastatin lactone. Pitavastatin also undergoes oxidative metabolism to form 8-hydroxy pitavastatin via cytochrome P450 (CYP) 2C9. Pitavastatin lactone and 8-hydroxy pitavastatin are the major and minor metabolite in the systemic circulation, respectively. Another minor oxidative metabolite is dihydroxy pitavastatin.

In vitro data show that CYPs 2C9 and 1B1 metabolize pitavastatin, whereas, CYPs 3A4, 2D6, 2C19, 2B6, 1A2, and 1A1 metabolize pitavastatin lactone. Pitavastatin inhibits CYP2C8 but does not inhibit CYPs 1A1, 1A2, 1B1, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, and 3A4 in vitro, whereas pitavastatin lactone does not inhibit CYPs 2C9 and 3A4 in vitro. There is no information on pitavastatin lactone's effect on other CYP isozymes.

Pitavastatin lactone's HMG-CoA reductase inhibition status is inconclusive.

Chiral inversion of pitavastatin via metabolism to its optical isomers may be very low per the dog and rat data.

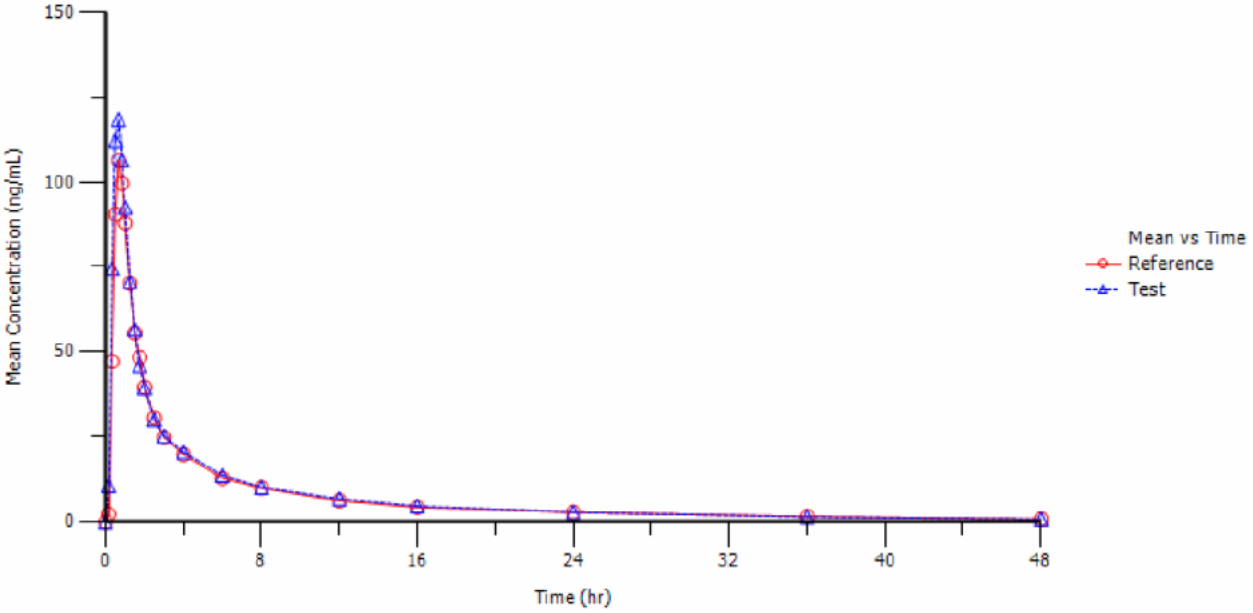
Excretion
In a mass-balance study, a mean of 15.1 and 78.6% of the dose was excreted in the urine and feces, respectively, with a mean total of 93.7% of the radioactive dose recovered in the excreta during 7 days postdose. The percentage of dose excreted in urine for pitavastatin, dihydroxy pitavastatin, pitavastatin glucuronide, pitavastatin lactone, and an unknown metabolite is 3, 4.1, 3.8, 0.8, and 1.2, respectively. The percentage of dose excreted in feces for pitavastatin, dihydroxy pitavastatin, pitavastatin lactone, 8-hydroxy pitavastatin, and an unknown metabolite is 42.9, 7.3, 2.6, 7.2, and 4.7, respectively.

Organic anion transporting polypeptide (OATP) 1B1 and 1B3 are responsible for the hepatic uptake of pitavastatin in vitro. The sponsor showed that pitavastatin is not a substrate of multidrug-resistance protein 1 (MDR1, alias P-gp) and multidrug resistance-associated protein 2 (MRP2) but is a substrate of breast cancer resistance protein (BCRP) in vitro. However, another research group showed that MDR1, MRP2, and BCRP are responsible for pitavastatin biliary excretion in vitro. Thus, the P-glycoprotein substrate status is inconclusive. The sponsor also showed that pitavastatin lactone is not a substrate of MRP2 and BCRP but is a substrate of MDR1 in vitro. Pitavastatin is neither a P-gp inhibitor nor a P-gp inducer in vivo.

2.3.2 What is the relative bioavailability between 4 mg pitavastatin tablets (magnesium salt) and 4 mg pitavastatin tablets (calcium salt)?

Study BA1386248 was a 2-treatment, 2-period, 2-sequence, and crossover study in healthy Asian men of 20 – 42 years (mean age 28 years), a weight range of 47.2 – 74.1 kg (mean: 58.9 kg), a height range of 155.5 – 174.0 cm (mean: 166.4 cm) and Body Mass Index (BMI) range of 18.7 – 26.9 kg/m^2 (mean: 21.3 kg/m^2). After an overnight fast (≥ 10 hours), each randomized participant received the test treatment of a 4 mg pitavastatin tablet (magnesium salt) in a period. After an overnight fast (≥ 10 hours), each randomized participant received the reference treatment of 4 mg pitavastatin tablet (calcium salt; LIVALO) in another period. The order of treatment administration was according to the randomization schedule. A washout of 11 days separated the 2 treatments. The sponsor collected serial plasma samples preodse and 48 hours postdose. The sponsor measured pitavastatin concentration in the plasma samples via validated bioanalytical method. Figure 2 shows the mean plasma pitavastatin concentration-time graphs for the test and reference.

Figure 2. Mean plasma pitavastatin concentration-time graphs for 4 mg pitavastatin tablet (magnesium salt; test) and 4 mg pitavastatin tablet (calcium salt; reference).



Source: Study BA1386248 study report Page 93/96

Table 3. Pitavastatin PK parameters of 4 mg pitavastatin tablet (magnesium salt).

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	27	128.997	39.856	30.897	53.530	198.100	130.400
AUCt	27	375.718	124.687	33.186	218.690	641.950	357.150
AUCi	27	390.997	131.716	33.687	223.320	673.120	374.100
Tmax	27	0.611	0.167	27.285	0.333	1.000	0.667
Kel	27	0.062	0.014	23.373	0.039	0.095	0.061
Thalf	27	11.838	2.799	23.644	7.327	17.819	11.314

Source: Study BA1386248 study report Page 41/96

Table 4. Pitavastatin PK parameters of 4 mg pitavastatin tablet (calcium salt).

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	27	114.936	32.284	28.089	54.750	172.200	113.000
AUCt	27	353.799	102.339	28.926	208.880	562.190	338.680
AUCi	27	371.032	110.466	29.773	214.630	594.100	352.140
Tmax	27	0.725	0.193	26.613	0.500	1.250	0.667
Kel	27	0.061	0.020	32.605	0.032	0.135	0.062
Thalf	27	12.387	3.771	30.448	5.122	21.525	11.261

Source: Study BA1386248 study report Page 41/96

Table 5. Statistical analysis of pitavastatin PK parameters of 4 mg pitavastatin tablet (magnesium salt) to 4 mg pitavastatin tablet (calcium salt).

PARAMETER	INTRA-SUBJECT CV(%)	RATIO OF GEOMETRIC MEANS	90% CI OF LOG TRANSFORMED DATA	POWER
AUCi	10.854	104.32%	(99.20%;109.71%)	1.0000
AUCt	9.971	105.11%	(100.36%;110.09%)	1.0000
Cmax	18.596	111.74%	(102.55%;121.74%)	0.9944

Source: Study BA1386248 study report Page 42/96

The pitavastatin C_{max} geometric mean ratio for 4 mg pitavastatin tablet (magnesium salt; test) and 4 mg pitavastatin tablet (calcium salt; reference) as well as those of pitavastatin AUC_{0-t} and AUC_{0-inf} is 111.7, 105.1, and 104.3%, respectively, Table 5. Thus, the 4 mg pitavastatin tablet (magnesium salt) is bioequivalent to the 4 mg pitavastatin tablet (calcium salt) under fasting conditions because all the 90% CIs of the geometric mean ratios are within the 80 and 125% bioequivalence goalpost.

This reviewer used the sponsor's pitavastatin PK parameters and reproduced identical results for the ratio of geometric means and their 90% CIs for pitavastatin C_{max}, AUC_t, and AUC_i between pitavastatin tablet (magnesium salt; test) and pitavastatin tablet (calcium salt; reference) via the software, Phoenix Version 1.4. This reviewer checked the percentage of extrapolated pitavastatin AUC from AUC_t to AUC_i. All extrapolated AUC are not > 13% of AUC_i for both test and reference and thus acceptable. The pitavastatin Thalf is consistent between pitavastatin tablet (magnesium salt) and pitavastatin tablet (calcium salt); see Tables 6 and 7.

The pitavastatin C_{max} geometric mean ratio (T/R) is 111.74% and its 90% CI is 102.55 – 121.74%. Because the upper bound of the 90% CI is close to the 125% bioequivalence goalpost, this reviewer checked whether there were errors that may affect the pitavastatin C_{max}. This reviewer found that all pitavastatin C_{max} did not have repeated bioanalytical analysis (Page 25 of Study BA1386248's report Appendix 16.5). Also none of the repeated measures before or after the pitavastatin t_{max} is greater than the pitavastatin C_{max}.

The original electronic data set "concentration-ba138624801.xpt" has only concentration data with no time data. Upon request, the sponsor submitted on June 12, 2015 the electronic data sets "conc-actual-ba-1386248-01-ba138624801.xpt" and "conc-nominal-ba-1386248-01-ba138624801.xpt" for the concentration-actual time data file and concentration-nominal time data file, respectively. This reviewer found that the sponsor used the actual time to calculate the elimination rate constant, KE, because the last 2 columns of "conc-actual-ba-1386248-01-ba138624801.xpt" was for "First time point for KE

calculation" and "Last time point for KE calculation," respectively, whereas the "conc-nominal-ba-1386248-01-ba138624801.xpt" file does not have these 2 columns. This reviewer further checked whether the sponsor used the nominal time or actual time to calculate AUC values. The nominal time and actual time of all plasma pitavastatin concentrations up to the 24 hours sample are identical except Participant 11, Period 2, Sequence 2, and Treatment 2 that the actual time is 1.08 hours and the nominal time is 1 hour. At nominal time of 36 hours, 5 participants had actual time that differed from nominal time (36.15, 37.133, 36.117, 36.367, and 36.367 hours). At nominal time of 48 hours, 14 participants had actual time that differed from nominal time (48.533, 48.133, 54.2, 50.317, 48.267, 48.1, 48.15, 48.283, 48.833, 48.05, 48.9, 48.3, and 55.283 hours). Majority of the data [(1+5+14)/1123; 1123 is the total number of plasma samples] show that the actual time and nominal time of plasma sample collection are identical. The plasma pitavastatin concentrations of the 2 last sampling time points (nominal time of 36 and 48 hours) are low as compared to the rest of the concentration-time profile (Figure 2). Thus, the AUC calculation through nominal time or actual time will likely not affect the bioequivalence assessment.

Pitavastatin tablets (magnesium salt) tested in Study BA1386248 are the same as the to-be-marketed pitavastatin tablets (magnesium salt; NDA 208-379's Cover Letter Page 5/8). The size of biobatch for pitavastatin tablets (magnesium salt) used in Study BA1386248 is (b) (4) tablets and the batch number is EMN268 (file: fp-coa-4mg-release.pdf). The batch size is larger than (b) (4) tablets and thus acceptable for bioequivalence assessment. The sponsor used the US-manufactured innovator 4 mg LIVALO tablets to conduct Study BA1386248 (Page 5 of Module 3.2.P.2 Pharmaceutical Development Report). The Orange Book lists 4 mg LIVALO tablet as the reference listed drug. The sponsor claimed that they kept all remaining test drug supplies as retention samples per the USFDA requirements. Study BA1386248's report Page 31/96 states Appendix 16.1.6 contains the accounting information of the retention samples. The sponsor did not hyperlink Appendix 16.1.6 but the submitted file "fasting-listing-of-pati-rece-test-ref-produ-ba138624801.pdf" is for Appendix 16.1.6. Retention of bioavailability and bioequivalence testing samples is a requirement for bioequivalence assessment (www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072869.pdf).

(b) (4) conducted the pivotal relative bioavailability study (BA1386248) and its bioanalytical work. The Office of Scientific Investigation and Surveillance (OSIS) inspected (b) (4) for another application on (b) (4) and concluded no action indicated (NAI). The NAI classification is good for 2 years. Unless there are concerns for the study or firm, OSIS may inspect the firm sooner than 2 years regardless of the NAI classification. NDA 208-379's data appear reasonable. Thus, OSIS does not plan to inspect (b) (4) for Study BA1386248.

2.3.3 How does food affect the bioavailability of 4 mg pitavastatin tablet (magnesium salt)?

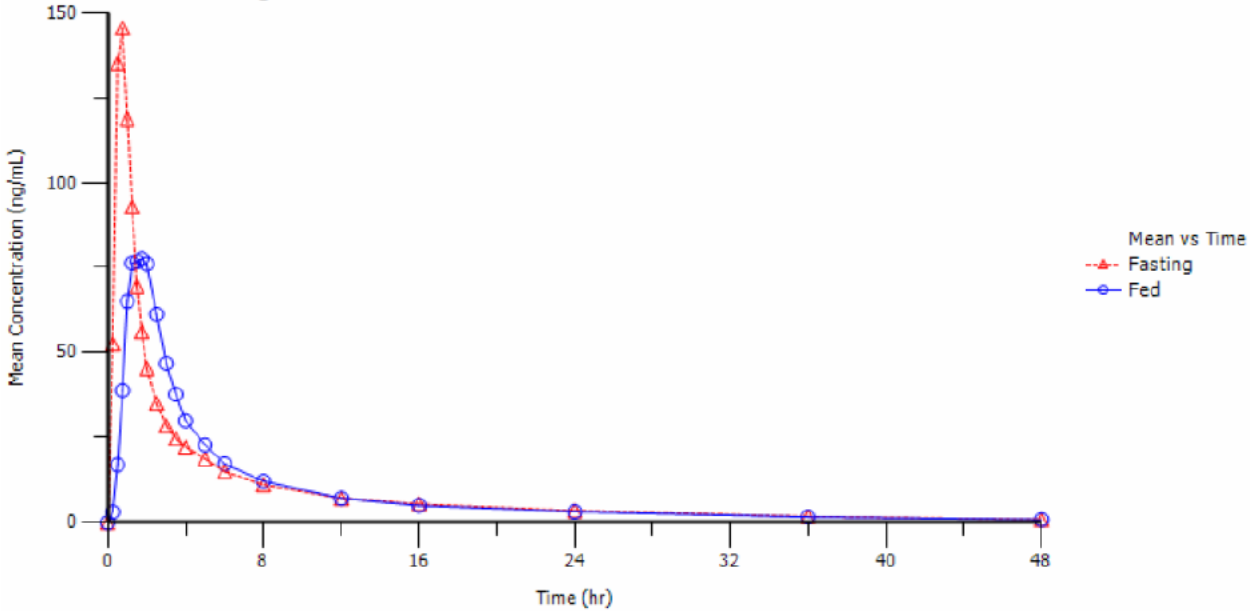
Study BA1386249 assessed the effect of food on the bioavailability of 4 mg pitavastatin tablet (magnesium salt). This was a 2-treatment, 2-period, 2-sequence, and crossover study in healthy Asian men of 18 – 43 years (mean: 30 years), a weight range of 46.6 – 79.6 kg (mean: 61.3 kg), a height range of 155.0 – 179.0 cm (mean: 167.5 cm) and BMI range of 18.6 – 26.5 kg/m^2 (mean: 21.8 kg/m^2). Each randomized participant orally received a 4 mg pitavastatin tablet (magnesium salt) after 1 of the following treatments in 2 different treatment periods:

- A: 10 hours overnight fast
- B: Each participant finished a standardized high-calorie and high-fat breakfast within 30 minutes and orally received the treatment 30 minutes after the breakfast.

Participants received each tablet with 240 mL ambient temperature water and fasted for at least 4 hours postdose. A washout of 7 days separated each treatment. The sponsor collected serial plasma samples predose and 48 hours postdose to determine pitavastatin concentration via validated bioanalytical method.

The 4 mg pitavastatin tablet (magnesium salt) batch number used in Study BA1386249 is EMN268. Figure 3 shows the mean plasma pitavastatin concentration-time graphs under fed and fasting conditions.

Figure 3. Mean plasma pitavastatin concentration-time data for 4 mg pitavastatin tablet (magnesium salt) under fed and fasting conditions.



Source: Study BA1386249 study report Page 94/97

Table 6. Pitavastatin PK parameters of 4 mg pitavastatin tablet (magnesium salt) under fed condition.

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	27	100.503	34.156	33.985	53.990	191.800	90.540
AUCt	27	411.962	159.126	38.626	183.420	901.190	381.720
AUCi	27	427.618	167.435	39.155	186.630	946.020	401.950
Tmax	27	1.481	0.444	29.941	0.750	2.500	1.500
Kel	27	0.065	0.023	35.660	0.043	0.159	0.059
Thalf	27	11.571	2.695	23.291	4.350	16.290	11.760
Tlag	27	0.102	0.143	140.497	0.000	0.500	0.000

Source: Study BA1386249 study report Page 41/97

Table 7. Pitavastatin PK parameters of 4 mg pitavastatin tablet (magnesium salt) under fasting condition.

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	27	169.143	80.233	47.435	78.550	456.600	158.300
AUCt	27	440.694	219.716	49.857	189.440	1325.600	387.170
AUCi	27	458.727	227.925	49.686	198.310	1368.000	396.510
Tmax	27	0.630	0.188	29.897	0.250	1.000	0.500
Kel	27	0.062	0.017	27.186	0.042	0.125	0.057
Thalf	27	11.767	2.460	20.906	5.530	16.460	12.190
Tlag	27	0.000	0.000	.	0.000	0.000	0.000

Source: Study BA1386249 study report Page 41/97

Table 8. Statistical analysis of pitavastatin PK parameters of 4 mg pitavastatin tablet (magnesium salt) under fed and fasting conditions.

PARAMETER	INTRA-SUBJECT CV(%)	RATIO OF GEOMETRIC MEANS	90% CI OF LOG TRANSFORMED DATA	POWER
AUCi	7.941	94.46%	(91.04%; 98.01%)	1.0000
AUCt	8.023	94.90%	(91.42%; 98.50%)	1.0000
Cmax	20.852	61.43%	(55.80%; 67.61%)	0.9837

Source: Study BA1386249 study report Page 42/97

Pitavastatin C_{max} geometric mean ratio under fed and fast conditions as well as that of AUC decreased 38.6 and about 5%, respectively, for the 4 mg pitavastatin tablet (magnesium salt). The 90% CI of fed to fasting pitavastatin AUC ratios are within the 80 – 125% bioequivalence assessment, whereas that for the pitavastatin C_{max} ratio is not.

Reviewer's Comments

Study BA1386249 has the following issues:

- There is a significant period effect of all pitavastatin PK parameters. However, the period effect is unlikely due to carryover of prior treatment because all the predose plasma pitavastatin concentrations were zero and no statistically significant carryover effects for any of the PK parameters exist. Since the analysis of variance model for the calculation of the point estimate for the test/reference ratio and 90% confidence interval (CI) took into consideration for the period and carryover effects, the results for the point estimate and 90% CI appear valid.
- The sponsor did not use the food effect guidance recommended high fat meal. The Guidance recommends a high-fat (50% of total caloric meal content) meal of 800 – 1000 calories, where 150, 250, and 500 – 600 calories are from protein, carbohydrate, and fat, respectively. Table 9 shows that the caloric content of the meal used in Study BA1386249 is consistent with the food effect guidance's recommendation and thus Study BA1386249's high-fat meal is acceptable.

Table 9. Composition of the non-standard breakfast meal used in Study BA1386249

Standard FDA Meal Used?		☐Yes ☑ NO				
Meal components and composition is listed in the table below						
Composition of Non-standard FDA Meal Used in Fed Study						
Ingredients		**Amount* (gm)**	**Energy (kcal)**	**Protein (kcal)**	**Fats (kcal)**	**Carbohydrate (kcal)**
Milk (Sterilised Flavoured)	Milk	200 mL	113.784	25.600	55.800	32.384
	Sugar	16	63.680	0.064	0.000	63.616
Mutton Cutlet	Mutton	80	94.400	68.480	25.920	0.000
	Potato	20	19.540	1.280	0.180	18.080
	Onion	20	10.020	0.960	0.180	8.880
	Bread	30	73.530	9.360	1.890	62.280
	Egg	60	103.740	31.920	71.820	0.000
	Oil	20 mL	180.000	0.000	180.000	0.000
Curry	Tomato	20	3.960	0.720	0.360	2.880
	Onion	40	20.040	1.920	0.360	17.760
	Curd	30	18.120	3.720	10.800	3.600
	Oil	10 mL	90.000	0.000	90.000	0.000
Bread Butter	Bread	20	49.020	6.240	1.260	41.520
	Butter	10	72.900	0.000	72.900	0.000
TOTAL			**912.734**	**150.264**	**511.470**	**251.000**
PERCENTAGE			**NA**	**16.463**	**56.037**	**27.500**

*Quantity of Raw Ingredients
Source: Table 2.7.1-82 of Module 2.7.1

- This reviewer notices that the sponsor reported "kcal" as the unit for energy, protein, fats, and carbohydrate in Table 9, whereas the food effect guidance refers to "calories" as the unit for energy, protein, carbohydrate, and fat. The Calories on a food package are actually kilocalories (1000 calories = 1 kilocalorie) (http://www.nutrition.gov/whats-food/commonly-asked-questions-faqs). For example, a can of soda containing 200 Calories contains 200,000 calories, or 200 kilocalories.
- Table 10 shows that the difference between the food effect on pitavastatin magnesium PK parameters and the food effect on pitavastatin calcium PK parameters is about 5% and relatively small. Thus, the label language for food effect on pitavastatin calcium may be applicable to that for pitavastatin magnesium and pitavastatin tablet (magnesium) can be taken with or without food.

Table 10. Food effect on pitavastatin tablet (magnesium salt) and pitavastatin tablet (calcium salt).

Pitavastatin Parameter	Pitavastatin Magnesium Food effect Geometric Mean Ratio and 90% Confidence Interval, %	Pitavastatin Calcium* Food effect Geometric Mean Ratio and 90% Confidence Interval, %
Cmax	61.43 (55.8 – 67.61)	56.91 (50.56 – 64.07)
AUC_{0-t}	94.46 (91.04 – 98.01)	89.00 (83.29 – 95.09)
$AUC_{0-\infty}$	94.9 (91.42 – 98.50)	89.34 (83.26 – 995.86)

*http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022363s000_ClinPharmR_P1.pdf
Source: Reviewer's table

2.4 Bioanalytical

Are the bioanalytical methods properly validated to measure pitavastatin in plasma samples?

The sponsor used a solid state extraction method and a liquid chromatography with tandem mass spectrometry (LC/MS/MS) assay to determine the pitavastatin concentration in plasma samples. Table 11 details the validation of the assay.

Table 11. Validation of the bioanalytical assay to measure pitavastatin in plasma samples.

Analyte	Pitavastatin
Matrix	Plasma
Anticoagulant	K3-EDTA
Sample volume, mL	0.5
Lower limit of quantitation, ng/mL	0.2
Linear range, ng/mL	0.2 – 200
Mean recovery (%) and precision (%CV)	
Pitavastatin	83.3 (0.7)
Fluvastatin (internal standard)	70.1 (4.4)
Assay precision (%CV of QC samples)	
Inter-day	6.1 – 9.0
Intra-day	1.2 – 10.6
Assay accuracy (% bias of QC samples)	
Inter-day	-4.1 – 0.1
Intra-day	-10.1 – 8.5

Source: This reviewer's compiled version of the sponsor's Study #BA1386248-Analytical Method Validation Report (5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies)

Total number of plasma samples for pitavastatin analysis is 1123. Total number of incurred samples reanalyzed is 112. Total number of reproducible incurred samples (within 20%) is 100.

The plasma samples were stable for at least 6 freeze and thaw cycles. The plasma samples were stable at room temperature for at least 25 hours. The extracted samples were stable at room temperature for at least 91 hours. All validations for the LC/MS/MS bioanalytical assay of pitavastatin appear acceptable with reasonable precision and accuracy.

3. Label Recommendations

Strikethrough text means deletion of the sponsor's proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

12.3 Pharmacokinetics

Absorption

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 ZYPITAMAG doses from 1 to 24 mg once daily. The absolute bioavailability of pitavastatin oral solution is 51%. Administration of a 4 mg ZYPITAMAG tablet with a high fat meal (50% fat content) decreases pitavastatin C_{max} by (b) (4) 39% 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. *See Question 2.3.3 for food effect Study BA1386249.*

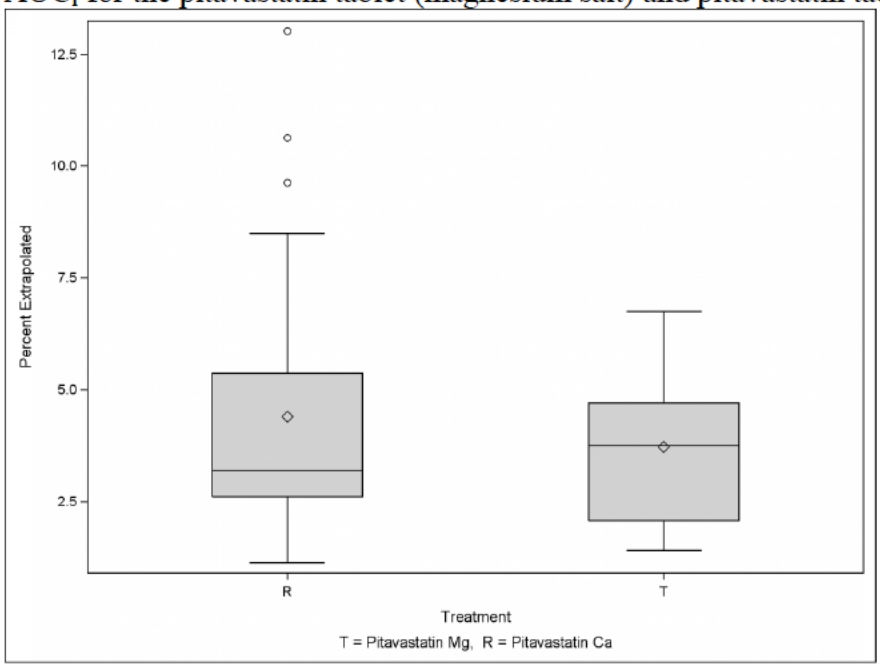
(b) (4)

(b) (4)

Internal Notes

For the pivotal relative bioavailability study (BA1386248), this reviewer also checked the percentage of extrapolated pitavastatin AUC from AUC_t to AUC_i divided by AUC_i and plotted their distribution (Figure below). All extrapolated AUC are not > 13% of AUC_i for both test and reference and thus acceptable.

Figure. Distribution of percentage of extrapolated pitavastatin AUC from AUC_t to AUC_i divided by AUC_i for the pitavastatin tablet (magnesium salt) and pitavastatin tablet (calcium salt).



Source: Reviewer's graph.

4 Appendix

4.1 Individual Study Synopsis

2.0 SYNOPSIS

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

Title of the study:

An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Pitavastatin Tablets 4 mg of Cadila Healthcare Limited, India and 'LIVALO®' (Pitavastatin) Tablets 4 mg of Kowa Pharmaceuticals America, Inc., USA and Lilly USA, USA in healthy adult human subjects under fasting conditions.

Investigators:

Principal Investigator: Dr. Mayur Soni, MBBS

Co- Investigators: Dr. Kanuji Thakor, MBBS
Dr. Nitin Dankhara, MBBS

Study Centers (Clinical, Analytical, PK and Statistical):

Clinical: Cliantha Research Limited
Opp. Pushparaj Towers, Nr. Judges Bungalows,
Bodakdev, Ahmedabad-380 054, Gujarat, India
Tel# +91-79-2685 3088-92, Fax# +91-79-2685 3093

Analytical: (b) (4)

PK and Statistical: Cliantha Research Limited
Sigma-1 Corporate, B/H. Rajpath Club,
Opposite Mann Party Plot,
Off. S.G Highway, Bodakdev,
Ahmedabad-380 054, Gujarat, India
Tel# +91-79-66135628, Fax# +91-79-66135602

Study Initiation Date:

Dosing Period I: 11 Sep 13

Dosing Period II: 22 Sep 13

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		
Analytical Start date: 04 Oct 13 Analytical End date: 14 Oct 13		
Study Completion Date: 24 Sep 13		

Objective:

The objectives of this study were to compare and evaluate the oral bioavailability of Pitavastatin Tablets 4 mg with that of 'LIVALO®' (Pitavastatin) Tablets 4 mg in healthy, adult, human subjects under fasting conditions and to monitor the safety of the subjects.

Methodology:

This open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions was conducted to compare and evaluate the oral bioavailability of two formulations of Pitavastatin Tablets 4 mg. The study was conducted with 28 (27 completed) healthy, adult, human subjects in accordance with Project No. BA1386248-01 (Version#01). In each study period, a single 4 mg oral dose of investigational product was administered to subjects following an overnight fast of at least 10 hours. The test formulation was Pitavastatin Tablets 4 mg of Cadila Healthcare Limited, India and the reference formulation was 'LIVALO®' (Pitavastatin) Tablets 4 mg of Kowa Pharmaceuticals America, Inc., USA and Lilly USA, USA. The subjects received the test product in one of the study period and the reference product in the other period; the order of administration was according to the randomization schedule. There was a 11-day interval between treatments.

Blood samples were collected at pre-dose (0.0 hours) and at intervals over 48.0 hours after administration of each dose. The plasma samples for all subjects of the study were delivered to the analytical laboratory at (b) (4) for the determination of Pitavastatin.

During the course of study safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests [hematology, biochemistry, immunological tests, urine analysis, Serum thyroid-stimulating hormone (TSH)], chest X-ray (within past six months) and ECG at baseline. Total creatin kinase, serum creatinine and serum magnesium tests were performed prior to check in of Period II. Laboratory parameters (hematology and biochemistry) were reassessed at the end of last period of the study.

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

Statistical analysis was performed on the pharmacokinetic data to compare the relative oral bioavailability of test formulation to the reference formulation by Cliantha Research Limited., Sigma-1 Corporate, B/H. Rajpath Club, Opposite Mann Party Plot, off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India. Bioequivalence was determined by a statistical comparison of AUCt, AUCi and Cmax for the test and reference products for Pitavastatin.

Number of Subjects:

- No. of subjects planned: 28
- No. of subjects dosed
  - Period I: 28
  - Period II: 27
- No. of subjects discontinued: 01 (Subject 10)
- No. of subjects completed: 27
- No. of subjects analyzed: 27
  - No. of subjects included in pharmacokinetic and statistical analysis: 27
  - No. of subjects analyzed in the bioanalytical laboratory for safety reasons: 00

Main Criteria for Inclusion:

Healthy adult, volunteers, 18 to 45 years old (both inclusive) with a Body Mass Index (BMI) 18.5 to 30.0 weight in kg / (height in meter)^2 both inclusive, who were Judged healthy on the basis of a pre-study physical examination and clinical laboratory tests.

Test Product T:

Name: Pitavastatin Tablet 4 mg (Magnesium Salt)
Batch No.: EMN268
Manufacturing Date: Mar 2013
Retest Date: Mar 2014
Dose: 4 mg, Mode of Administration: Oral

Reference Product R:

Name: Livalo® (Pitavastatin) Tablet 4 mg (Label Claim: Each tablet contains 4.18 mg of Pitavastatin calcium equivalent to 4 mg Pitavastatin)
Lot No.: 3102666
Expiry Date: Jun 2015
Dose: 4 mg, Mode of Administration: Oral

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

Duration of Treatment:

In each period, single oral dose of Pitavastatin Tablets 4 mg was administered to the subjects under fasting condition. Each dose was separated by a 11-day interval. Total duration of the treatment from first subject dosed to last subject completed was 13 days.

Analytical Method: Plasma samples were assayed by validated LC/MS/MS method developed at (b) (4). The analytical method was validated over a concentration range of 0.2000 ng/mL to 200.0 ng/mL for Pitavastatin.

The complete Bioanalytical report is appended in appendix-16.5.

Pharmacokinetic Analysis:

- Primary pharmacokinetic parameters: AUCt, AUCi & Cmax
- Secondary pharmacokinetic parameters: Tmax, Kel & tHalf
- Software: WinNonlin® professional software and SAS® statistical software
- No. of subjects included in pharmacokinetic analysis: 27

Statistical Methods: The analytical data was used to calculate the pharmacokinetic parameters: Cmax, AUCt, AUCi, Tmax, Kel and tHalf using a non-compartmental analysis of WinNonlin® professional software.

Criteria for evaluation: These pharmacokinetic parameters were evaluated statistically by using the PROC Mixed procedure from SAS® statistical software.

Table 1: Summary of Pharmacokinetic Data for Pitavastatin (n=27)

Dose: 4 mg

(Reference Product: Livalo® (Pitavastatin) Tablet 4 mg)

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.hr/ mL)	353.799	102.339	28.926
AUCi (ng.hr/ mL)	371.032	110.466	29.773
Cmax (ng/ mL)	114.936	32.284	28.089

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

(Test Product: Pitavastatin Tablet 4 mg (Magnesium Salt))

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.hr/ mL)	375.718	124.687	33.186
AUCi (ng.hr/ mL)	390.997	131.716	33.687
Cmax (ng/ mL)	128.997	39.856	30.897

Table 2: Test & Reference Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for Pitavastatin (n=27)

Pharmacokinetic parameter	Geometric mean (Test)	Geometric mean (Reference)	Ratio (%)
AUCt (ng.hr/ mL)	357.655	340.252	105.11
AUCi (ng.hr/ mL)	371.574	356.173	104.32
Cmax (ng/ mL)	123.111	110.181	111.74
Pharmacokinetic parameter	**90% Confidence Intervals**	**Intra-Subject CV (%)**	**Power**
AUCt (ng.hr/ mL)	(100.36%;110.09%)	9.971	1.0000
AUCi (ng.hr/ mL)	(99.20%;109.71%)	10.854	1.0000
Cmax (ng/ mL)	(102.55%;121.74%)	18.596	0.9944

Safety Results:

Adverse Events: The data on adverse events were collected and tabulated.

Clinical Lab tests: The safety related laboratory tests [hematology, biochemistry, immunology, urine analysis, Serum thyroid-stimulating hormone (TSH)], ECG and chest X-ray (within six months) were carried out on the study subjects during the time of screening. Total creatin kinase, serum creatinine and serum magnesium tests were performed prior to check in of Period II. Laboratory parameters (hematology and biochemistry) were reassessed at the end of last period of the study. However, in this study, all the out of range laboratory parameters were evaluated as clinically insignificant and clinically significant during post study assessment. The laboratory parameter which was labeled as clinically significant by the physician, was documented as an adverse event (Refer to Appendix 16.2.7) and repeated until it was reported within the normal range in the follow up.

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

SUMMARY OF RESULTS: For the log transformed Pitavastatin data, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80% to 125% limits for AUCt (100.36%;110.09%), AUCi (99.20%;109.71%) and Cmax (102.55%;121.74%). (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products– General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003). See Section 11.4.7 for more detail.

CONCLUSION: Based on these results, Pitavastatin Tablet 4 mg (Magnesium Salt) by Cadila Healthcare Ltd., India and Livalo® (Pitavastatin) Tablet 4 mg (Label Claim: Each tablet contains 4.18 mg of Pitavastatin calcium equivalent to 4 mg Pitavastatin), Mfg. by Patheon Inc. Cincinnati, OH 45237 USA or by Kowa Company, Ltd Nagoya-462-0024, Japan, Mkt. by Kowa Pharmaceuticals America, Inc. Montgomery, AL 36117 USA and Lilly USA, LLC. Indianapolis, IN 46285, USA, are bioequivalent under fasting conditions.

Date of Report: 09 Nov 13

2.0 SYNOPSIS

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

Title of the study: An Open Label, Randomized, Two-Period, Two Treatment (Fed Vs. Fasting), Two-Sequence, Crossover, Balanced, Single Dose Food Effect Bioavailability Study Of Pitavastatin Tablets 4 mg Of Cadila Healthcare Limited, India In Healthy Adult Human Subjects Under Fasting And Fed Conditions.

Investigators:
Principal Investigator: Dr. Manish Singhal, MBBS
Co- Investigator: (b) (4);

Study Centers (Clinical, Analytical, PK and Statistical):

Clinical:
Cliantha Research Limited
Sigma-1 Corporate,
B/H. Rajpath Club,
Opposite Mann Party Plot,
Off. S.G Highway, Bodakdev,
Ahmedabad-380 054,Gujarat, India
Tel# +91 -79 – 66135601
Fax# +91 -79 – 66135602

Analytical: (b) (4)

Pharmacokinetic And Statistical:
Cliantha Research Limited
Sigma-1 Corporate,
B/H. Rajpath Club,
Opposite Mann Party Plot
Off. S.G Highway, Bodakdev,
Ahmedabad.-380 054, Gujarat, India
Tel# +91-79-66135628
Fax# +91-79-66135602

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg NAME OF ACTIVE INGREDIENT: Pitavastatin	VOLUME: PAGE:	

Study Initiation Date:

Dosing Period I: 25 Sep 13

Dosing Period II: 02 Oct 13

Analytical Start date: (b) (4)

Analytical End date:

Study Completion Date: 04 Oct 13

Objectives:

The objectives of this study were to compare and evaluate the oral bioavailability of Pitavastatin Tablets 4 mg in healthy, adult, human subjects under fasting and fed conditions and to monitor the safety of the subjects.

Methodology:

This open label, randomized, two-period, two treatment (Fed Vs. Fasting), two-sequence, crossover, balanced single dose food effect oral bioavailability study in healthy, adult, human subjects under fasting and fed conditions was conducted to compare and evaluate the oral bioavailability of Pitavastatin Tablets 4 mg. The study was conducted with 28 (27 completed) healthy, adult, human subjects in accordance with Project No. BA1386249-01 (Version#01). In each study period, a single 4 mg oral dose of test product was administered to subjects at about 30 minutes after serving of standardized high calorie and high fat breakfast for fed condition and a single 4 mg oral dose of test product was administered to subjects following an overnight fast of at least 10 hours for fasting condition. The test formulation was Pitavastatin Tablets 4 mg of Cadila Healthcare Limited, India. The subjects received the test product under fasting condition in one period and under fed conditions in the other period as per randomization schedule. There was a 07-day interval between treatments.

Blood samples were collected pre-dose (0.0 hours) and at intervals over 48.0 hours after administration of each dose. The plasma samples for all subjects of the study were sent to the analytical laboratory at (b) (4) for the determination of Pitavastatin.

During the course of study safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests [hematology, biochemistry, immunological

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

tests, urine analysis and Thyroid function tests (TSH)] chest X-ray (within past six months) and ECG at baseline. Total creatin kinase, serum creatinine and serum magnesium tests were performed prior to check in of Period II. Laboratory parameters (hematology and biochemistry) were reassessed at 48.0 hours post dose of the last study period.

Statistical analysis was performed on the pharmacokinetic data to compare the relative oral Food Effect bioavailability of test formulation by Cliantha Research Limited., Sigma-1 Corporate, B/H. Rajpath Club, Opposite Mann Party Plot, off. S.G. Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India. Food Effect bioavailability was determined by a statistical comparison of AUCt, AUCi and Cmax for the test product in fasting and fed Conditions for Pitavastatin.

Number of Subjects:

- No. of subjects planned: 28
- No. of subjects dosed
  - Period I: 28
  - Period II: 27
- No. of subjects discontinued: 01
- No. of subjects completed: 27
- No. of subjects analyzed: 27
  - No. of subjects included in pharmacokinetic and statistical analysis: 27

  No. of subjects analyzed in the bioanalytical laboratory for safety reasons: 00

Main Criteria for Inclusion:

Healthy adult, human volunteers, 18 to 45 years old (both inclusive) with a Body Mass Index (BMI) 18.5 to 30.0 weight in kg / (height in meter)^2 both inclusive, who were judged healthy on the basis of a pre-study physical examination and clinical laboratory tests.

Test Product T:

Name: Pitavastatin Tablet 4 mg (Magnesium salt)
Batch No.: EMN268
Manufacturing date: Mar 2013
Retest date: Mar 2014
Dose: 4 mg, Mode of Administration: Oral

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

Duration of Treatment:

In each period, single oral dose of Pitavastatin Tablets 4 mg was administered to the subjects under fasting and fed condition. Each dose was separated by a 07-day interval. Total duration of the treatment from first subject dosed to last subject completed was 09 days.

Analytical Method: Plasma samples were assayed by validated LC/MS/MS method developed at (b) (4) . The analytical method was validated over a concentration range of 0.2000 ng/mL to 200.0 ng/mL for Pitavastatin.

The complete Bioanalytical report is appended in appendix-16.5.

Pharmacokinetic Analysis:

- Primary pharmacokinetic parameters: AUCt, AUCi & Cmax
- Secondary pharmacokinetic parameters: Tmax, Tlag, Kel & tHalf
- Software: WinNonlin® professional software and SAS® statistical software
- No. of subjects included in pharmacokinetic analysis: 27

Statistical Methods: The analytical data was used to calculate the pharmacokinetic parameters: Cmax, AUCt, AUCi, Tmax, Tlag, Kel and tHalf using a non-compartmental analysis of WinNonlin® professional software.

Criteria for evaluation: These pharmacokinetic parameters were evaluated statistically by using the PROC Mixed procedure from SAS® statistical software.

Table 1: Summary of Pharmacokinetic Data for Pitavastatin (n=27)

Dose: 4 mg

(Test Product: Pitavastatin Tablet 4 mg (Magnesium salt)) – Fasting Condition

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.hr/ mL)	440.694	219.716	49.857
AUCi (ng.hr/ mL)	458.727	227.925	49.686
Cmax (ng/ mL)	169.143	80.233	47.435

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

(Test Product: Pitavastatin Tablet 4 mg (Magnesium salt)) – Fed Condition

Pharmacokinetic parameter	Arithmetic mean	Standard deviation	Coeff of Variation (%)
AUCt (ng.hr/ mL)	411.962	159.126	38.626
AUCi (ng.hr/ mL)	427.618	167.435	39.155
Cmax (ng/ mL)	100.503	34.156	33.985

Table 2: Fasting & Fed Geometric mean, Ratio, 90% Confidence Intervals, Intra-Subject CV (%) and Power based on Log-transformed data for Pitavastatin (n=27)

Pharmacokinetic parameter	Geometric mean (Fasting)	Geometric mean (Fed)	Ratio (%)
AUCt (ng.hr/ mL)	405.387	384.695	94.90
AUCi (ng.hr/ mL)	422.006	398.626	94.46
Cmax (ng/ mL)	155.097	95.270	61.43
Pharmacokinetic parameter	**90% Confidence Intervals**	**Intra-Subject CV (%)**	**Power**
AUCt (ng.hr/ mL)	(91.42%; 98.50%)	8.023	1.0000
AUCi (ng.hr/ mL)	(91.04%; 98.01%)	7.941	1.0000
Cmax (ng/ mL)	(55.80%; 67.61%)	20.852	0.9837

Safety Results:
Adverse Events: The data on adverse events were collected and tabulated.

Clinical Lab tests: The safety related laboratory tests [hematology, biochemistry, immunology, urine analysis and Thyroid function tests (TSH)] were carried out on the study subjects during screening and reassessed (hematology and biochemistry) at 48.0 hours post dose of the last study period. Total creatin kinase, serum creatinine and serum magnesium tests were performed prior to check in of Period II. However, in this study, all the out of range laboratory parameters

NAME OF SPONSOR: Cadila Healthcare Limited, India	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT: Pitavastatin Tablets 4 mg	VOLUME: PAGE:	
NAME OF ACTIVE INGREDIENT: Pitavastatin		

were evaluated as clinically insignificant and clinically significant during post study assessment. The laboratory parameter which was labeled as clinically significant by the physician was documented as an adverse event (refer to Appendix 16.2.7) and repeated until it was reported clinically non significant in the follow up.

ABSENCE OF FOOD EFFECT: For the log transformed Pitavastatin data, the 90% confidence intervals about the (Fed/Fasting) ratios of the geometric mean are within the 80.00% to 125.00% limits for AUCt (94.90%) and AUCi (94.46%) but not for Cmax (61.43%). (set by FDA, Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products– General Considerations*, Center for Drug Evaluation and Research [CDER], March, 2003). See Section 11.4.7 for more detail.

CONCLUSION: Based on these data, Pitavastatin Tablet 4 mg (Magnesium salt) by Cadila Healthcare Ltd., India, Food effect observe in Cmax but not in AUCt and AUCi.

Date of Report: 15 Nov 13

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

/s/

SZE W LAU
12/09/2015

JAYABHARATHI VAIDYANATHAN
12/09/2015

ADDENDUM to CLINICAL PHARMACOLOGY FILING REVIEW

NDA	208-379
Submission Date	March 31, 2015
Brand Name	To be determined
Generic Name	Pitavastatin magnesium
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader (Acting)	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Zydus Pharmaceuticals
Formulation; Strength	Immediate release oral tablets; 1, 2, and 4 mg
Indication	Adjunct therapy to diet to reduce elevated lipid concentrations

This addendum updates the Clinical Pharmacology filing review of NDA 208-379 dated May 11, 2015 in DARRTS.

The sampling time data for plasma pitavastatin concentrations measurements in the electronic "concentration.xpt" files of the 2 Clinical Pharmacology studies [bioequivalence (BA1386248) and food-effect (BA1386249)] are missing. This reviewer did not notice this issue when checking these files for filing because this will be part of the review effort later. Also, electronic demographic data of participants are not available. These missing data are available in the study reports and bioanalytical reports. However, complete electronic datasets for the 2 Clinical Pharmacology studies are essential for the review of NDA 208-379. Thus, the sponsor needs to receive the following information request.

Information Request to the Sponsor
Provide the following information in electronic SAS transport files (.xpt) format for Studies BA1386248 and BA1386249:

- the nominal time to collect the plasma samples for the determination of pitavastatin concentrations for each participant in each study because the sampling time data for plasma pitavastatin concentrations measurements in the electronic "concentration.xpt" file are missing
- the actual time to collect the plasma samples for the determination of pitavastatin concentrations for each participant in each study because the sampling time data for plasma pitavastatin concentrations measurements in the electronic "concentration.xpt" file are missing
- demographic data of all study participants in each study because there is no electronic file for the demographic data

---

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

/s/

SZE W LAU
05/26/2015

JAYABHARATHI VAIDYANATHAN
05/26/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208-379	**SDN**	1
Applicant	ZYDUS PHARMACEUTICALS	**Submission Date**	March 31, 2015
Generic Name	Pitavastatin magnesium	**Brand Name**	
Drug Class	Statin		
Indication	Treat hyperlipidemia or mixed dyslipidemia		
Dosage Regimen	1 mg to 4 mg once daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	2	**OND Division**	DMEP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	S.W. Johnny Lau	Jaya Vaidynathan	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	5/29/2015	**74-Day Letter Date**	5/29/2015
Review Due Date	12/30/2015	**PDUFA Goal Date**	1/29/2016

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: Bioequivalent study (BA1386248) is the pivotal clinical study for the entire NDA 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			Study BA1386248
☑ Food Effect			Study BA1386249
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose		Studies BA1386248 and BA1386249
	☐ 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**		**In Vivo**	2
Total Number of Studies to be Reviewed				2

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	See Filing Memo on this review's last page.
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	Submitted pharmacokinetic data
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

Is the 4 mg pitavastatin magnesium tablets tested in the bioequivalence study (BA1386248) and food-effect study (BA1386249) the same as the to-be-marketed 4 mg pitavastatin magnesium tablets?
Yes. The sponsor used Exhibit Batch EMN268 (4 mg pitavastatin tablets) to conduct Studies BA1386248 and BA1386249. The submission cover letter's Page 6/8 shows the Exhibit Batch numbers used in these 2 studies. The Pharmaceutical Development Report Section 3.2.P.2, Subsection 2.3.10, Page 131/160 shows the formulation of the Exhibit Batch. The Description and Composition of the Drug Product Section 3.2.P.1, Page 5/12 shows the formulation of the to-be-marketed product (4 mg pitavastatin tablets).

Need for Clinical Trial Inspection

Study BA1386248 is the pivotal study that shows bioequivalence between the pitavastatin magnesium tablets and the pitavastatin calcium tablets. Thus, an OSI inspection on Study BA1386248 (An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Pitavastatin Tablets 4 mg of Cadila Healthcare Limited, India and 'LIVALO®' (Pitavastatin) Tablets 4 mg of Kowa Pharmaceuticals America, Inc., USA and Lilly USA, USA in healthy adult human subjects under fasting conditions.) is appropriate.
Study BA1386248's Clinical Facility:
Cliantha Research Limited
Opp. Pushparaj Towers
Nr. Judges Bungalows
Bodakdev, Ahmedabad-380 054
Gujarat, India
Tel# +91 – 79 – 2685 3088 – 92
Fax# +91 – 79 – 2685 3093

Study BA1386248's Analytical Facility:
(b) (4)

Filing Issue

The Division of Metabolism and Endocrinology Products plans to refuse to file NDA 208-379 because the sponsor failed to address the requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) through submission of an initial PSP as described in section 505B(e) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Food and Drug Administration Safety and Innovation Act (FDASIA).

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

/s/

SZE W LAU
05/11/2015

JAYABHARATHI VAIDYANATHAN
05/11/2015